EYE ON THE BAYOU
NEW CONCEPTS IN GLAUCOMA, CATARACT
AND NEURO-OPHTHALMOLOGY
EYE ON THE BAYOU
NEW CONCEPTS IN
GLAUCOMA, CATARACT
AND NEURO-
OPHTHALMOLOGY

edited by Jonathan D. Nussdorf

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of the New Orleans Academy of Ophthalmology,
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Preface

The 54th annual symposium of the New Orleans Academy of Ophthalmology was held February 18-20, 2005. This Academy meeting was devoted to current topics pertaining to glaucoma, cataract surgery and neuro-ophthalmology. The meeting consisted of formal lectures, roundtable discussions with questions from the audience and workshop presentations.

I have deep appreciation for those who serve as mentors to us and participated in this meeting, they help to elevate the level of care we provide to our patients. Their active participation made this meeting worthwhile. I would like to acknowledge our sponsors for providing unrestricted financial support, which helped to defray the expense of this medical education meeting and subsequent publication. Sincere thanks go to those who participated on the Program Committee and special acknowledgement is given to Dr. Scott Lanoux, President of the New Orleans Academy of Ophthalmology and Amber Howell, Executive Director for their hard work in organizing this symposium.

Jonathan D. Nussdorf, MD
Program Chairman
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I make progress by having people around me who are smarter than I am and listening to them. And I assume that everyone is smarter about something than I am.

Henry J. Kaiser
President’s letter

On behalf of the Board of Directors of the New Orleans Academy of Ophthalmology, I would like to congratulate and give my sincerest thanks to the program committee and program chair for the success of the 54th Annual Symposium, February 18-20, 2005. Each year I continue to marvel at the quality of the faculty and the program, and this year was no exception. The end result of such excellence culminates with this volume of NOAO Transactions. The editor, Dr Jonathan Nussdorf, has put together an outstanding text derived from the various lectures, roundtables and question and answer sessions that will serve as an important reference in ophthalmologic literature for the benefit of the ophthalmologic community for years to come.

I would also like to draw attention to the Eye, Ear, Nose and Throat Foundation, without whose generous support neither the transactions nor the symposium would be possible. The Foundation was created in 1981 to support The Eye, Ear, Nose and Throat Hospital, which was founded in 1889 for the purpose of providing medical care to the indigent population of New Orleans. Their mission is to provide funding for medical research and education for ophthalmology and otolaryngology as well as direct patient care.

As president of the NOAO, I have been extremely fortunate to have such a dedicated board of directors and staff. Their energy and passion towards providing quality ophthalmic education to the region cannot be understated. Our Executive Director, Amber W. Howell, has been an integral part of this organization and of the success of the Symposium for the past four years, and I commend her for her dedication and drive.

Finally, I would like to thank Kugler Publications for their editorial expertise over the many years. However, the true success of this symposium and the subsequent transactions would not have been possible without the enthusiastic and continuing support of the ophthalmologists of New Orleans and the Gulf Coast who are members of the Academy. To them, I give my appreciation.

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Ten easy mistakes to avoid in your next neuro-ophthalmic patient

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Introduction

The busy comprehensive ophthalmologist is confronted by many rapid and important clinical decisions every day. Mixed in among the routine refractions and ‘red eyes’ however might be vision-threatening or life-threatening neuro-ophthalmic disease. This manuscript will review some practical recommendations for avoiding the common mistakes in the evaluation of the neuro-ophthalmic patient (see Table 1). A case based format will emphasize key points.

Case one

A 45-year-old white female presents with headache and the acute onset loss of vision in the left eye (OS). The technician checks the vision at 20/15 OD and 20/25+ OS, records ‘PERRLA’ (pupils, equal, round, reactive to light and accommodation) for the pupil exam, and dilates the patient. Slit lamp biomicroscopy shows a mild nuclear cataract OS. The physician performs the remainder of the exam and finds a normal macula and optic nerve OU. A diagnosis of ‘cataract OS is made and the patient is given a follow-up appointment for ‘six months. The patient returns in three months with the same complaint and the exam is unchanged. An automated visual field is ‘unreliable’ because of a high false positive and high false negative rate, multiple fixation losses, and poor patient performance. A diagnosis of ‘worsening cataract’ is made and the patient is given a six-month appointment.

The patient seeks a second opinion and the visual acuity is now 20/15 OD and 20/40 OS. There is a left relative afferent pupillary defect (RAPD). The slit lamp exam shows a nuclear cataract but not compatible with 20/40 acuity OS. The fundus exam now shows trace temporal pallor of the optic disc OS. The visual field
Table 1. Ten recommendations for avoiding errors in neuro-ophthalmic patients

1. Check for the relative afferent pupillary defect (RAPD) in every patient with unexplained visual loss (Don’t use ‘PERRLA’ alone to document pupil exam).
2. Don’t assume that 20/20 visual acuity excludes an optic neuropathy.
3. Perform a formal visual field (e.g., automated or Goldmann perimetry) in every unexplained vision loss if possible and correlate visual field loss to presumed ocular etiology.
4. Compare the temporal and nasal field carefully for any evidence for hemianopic field loss (i.e., the vertical step, junctional, homonymous or bitemporal loss).
5. Recognize that an ‘unreliable’ visual field does not equal a ‘normal’ visual field and perform a careful confrontation field with attention to the vertical meridian in patients unable to complete a reliable formal visual field test.
6. Look at the slit lamp exam after dilation and consider retinoscopy.
7. Remember that a normal appearing macula does not equal a normal functioning macula (e.g., cone dystrophy, other subtle or occult maculopathies) and consider the use of electrophysiology to test retinal function in these cases (e.g., multifocal or full field electroretinography).
8. Be aware that a normal appearing optic nerve does not equal a normally functioning optic nerve (i.e., retrobulbar optic neuropathy).
9. Beware a normal appearing optic nerve and an ipsilateral RAPD as this clinical situation is more not less likely to be a compressive optic neuropathy.
10. Recall that optic atrophy is not a diagnosis and is simply an ophthalmoscopic description. Although many causes are benign, it could be a sign of a potentially vision or life threatening etiology.

shows a superotemporal visual field loss OD and central depression with breakout to the temporal periphery OS. Magnetic resonance imaging shows a large suprasellar mass (Fig. 1). The tumor is removed but the vision does not recover. What went wrong? How can we avoid making the same error?

Fig. 1. Coronal T1 weighted magnetic resonance imaging shows a suprasellar mass with compression of the optic chiasm and optic nerves.
Ten easy mistakes to avoid in your next neuro-ophthalmic patient

Table 2. Common causes for unilateral visual loss without a relative afferent pupillary defect (RAPD)

1. Media (e.g., subtle oil droplet or posterior subcapsular cataract, keratoconus) or refractive (e.g., irregular astigmatism) etiology.
2. Macula (e.g., epiretinal membrane, cystoid macular edema, macular hole, central serous retinopathy).
3. ‘Making it up’ (i.e., non-organic visual loss).
4. ‘Missed it’ (e.g., ‘PERRLA’, physician did not check pupil personally, subtle RAPD).
5. Monocular complaints but binocular and symmetric afferent disease.

Check for the relative afferent pupillary defect

Unexplained visual loss is a common presenting symptom to the comprehensive ophthalmologist. Unfortunately, in a very busy practice checking the pupil is often a task delegated completely to the ophthalmic technician. While this strategy might be more time efficient, the clinician should consider instructing the technicians to call the physician for the ‘tough ones (i.e., questionable relative afferent pupil defect, anisocoria in patient with diplopia or ptosis). If the patient with unexplained visual loss has already been dilated prior to the physician encounter then the patient could simply return the next day for a quick (‘pupil check’) follow-up appointment. The relative afferent pupillary defect (RAPD) can be the only objective sign of a retrobulbar optic neuropathy or occult retinopathy. The widely used abbreviation ‘PERRLA’ (i.e., pupils equal, round, reactive to light and accommodation) does not include an assessment of the RAPD and I would urge that PERRLA not be used as the sole documentation of the pupil exam. The absence of a RAPD in unilateral unexplained visual loss is a very reassuring finding, but it should be confirmed personally by the physician. The differential diagnosis for a truly unilateral loss of vision and no ipsilateral RAPD is listed in Table 2. Bilateral and symmetric visual loss may also present with a subtle or absent RAPD because the test relies upon the pupillary response relative to the fellow eye (the ‘R’ in RAPD). At the University of Iowa’s H. Stanley Thompson Neuro-ophthalmology Clinic, neutral density filters (e.g., 0.3, 0.6, 0.9, 1.2 log unit filters) are used to quantify the RAPD. These filters are available in photography stores or can be obtained commercially (i.e., neutral density filter sets or bars). Patients with a subtle or questionable RAPD can be ‘neutralized’ by placing the smaller (e.g., 0.3 log unit) filter in front of the ‘good’ eye and performing the traditional swinging flashlight test. Placing the 0.3 log unit filter over the suspected ‘bad’ eye can bring out a subtle RAPD. In the case above, the patient was brought back to clinic the next morning for a ‘pupil check’ and a subtle 0.3 log unit left RAPD was detected.

Don’t assume that 20/20 visual acuity is normal

Although 20/20 visual acuity is considered ‘normal’ vision, many optic neuropathies can present with normal visual acuity (e.g., glaucoma, disc drusen, and papilledema). In addition, a patient with 20/15 vision OD who reads the Snellen line
rapidly and fluently may on the other hand read with the left eye the 20/20 line very slowly and with lots of guessing and effort. In this setting, 20/20 vision is not normal. Recording the speed and effort of the visual acuity provides important subjective information that might suggest a subtle afferent abnormality (e.g., ‘20/15 fast OD, 20/20, slow with effort and lots of guesses OS’). In addition, patients without papillomacular bundle involvement and a bitemporal or homonymous hemianopsia may have 20/20 acuity OU.

Patients should be specifically questioned regarding the exact nature, circumstance, and location of their visual complaint. Double vision (e.g., ocular misalignment), oscillopsia (e.g., nystagmus), reading difficulty (e.g., convergence or accommodative problems), or visual processing or neurocognitive abnormalities (e.g., alexia, prosopagnosia, cerebral dyschromatopsia) may all be described by the patient as ‘blurred vision’ despite 20/20 visual acuity.

Perform a formal visual field in every unexplained visual loss

Visual field testing by confrontation is a reasonable screening test that should be performed in every new patient. The sensitivity and specificity of confrontation testing however are quite variable depending on the reliability of the patient and the skill and experience of the examiner. Shahinfar et al. prospectively compared confrontation visual field testing with full-threshold Humphrey automated static perimetry 24-2 or 30-2. The sensitivity of confrontation testing varied depending on type of visual field loss: 51% for arcuate scotomas, 67% for visual field constriction, 78% for altitudinal scotomas, and 90% for hemianopias. On the other hand, Johnson and Baloh reported that confrontation visual field testing was fairly insensitive (20% to 50% sensitivity) for arcuate scotomas and bitemporal hemianopsia.

It is my opinion that a formal visual field should be performed on every patient with unexplained visual loss. Attributing the visual loss to a ‘red herring’ found on the exam (e.g., cataract or age-related macular degeneration) is another common error. Clinicians should make a special effort to clinically correlate the pathologic finding with the size, severity, and location of the proposed etiology for visual loss. The formal visual field is especially helpful in this regard because patients often have multiple concomitant anterior or posterior segment findings that might be coincidental (e.g., cataract). For example, if a patient has presumed age related macular degeneration as the cause for ‘counting fingers’ vision, the visual field should demonstrate an ipsilateral central scotoma that matches the size, shape, and density of the retinal pathology (i.e., the field defect should not be hemianopic or involve peripheral visual field loss). Likewise, cataract, media opacities, and refractive error would be expected to produce diffuse depression of the visual field and not focal or hemianopic field loss. Finally, the visual field should be tested in both eyes as patients with unilateral complaints may actually have bilateral findings.
Ten easy mistakes to avoid in your next neuro-ophthalmic patient

Compare the nasal and temporal fields for hemianopic loss

Formal visual field testing of both eyes is important to detect subtle abnormalities in the fellow eye and to allow comparison of the nasal and temporal hemifields. For example, at the junction of the optic nerve and chiasm, the nasal fibers that are crossing are dissociated from the uncrossed temporal fibers. A lesion at the junction can therefore produce a superotemporal field defect in the contralateral and asymptomatic fellow eye (the junctional scotoma) in addition to the ipsilateral field loss due to the optic neuropathy. A monocular and hemianoptic (nasal or temporal) field loss can also occur at the junction (i.e., the junctional scotoma of Traquair). Recognition of these junctional visual field defects is important because a lesion of the junction is often compressive in nature and neuroimaging is strongly recommended.

Comparison of the nasal and temporal hemifields is critical for the detection of homonymous field loss. Any unexplained bitemporal flavor to the visual field defect should be considered to be chiasmal in origin until proven otherwise. Likewise, any homonymous flavor to the visual loss should suggest retrochiasmal involvement. Any hemianoptic character (i.e., respect of the vertical meridian) to the field loss is significant and the clinician should not be swayed from the diagnosis by drift across the vertical meridian in other locations. In other words, a vertical step is evidence for a possible intracranial etiology. Unfortunately published examples of bitemporal and homonymous visual field loss (i.e., 'book fields') often do not look like 'real world' visual fields. This 'publication bias' occurs because authors of textbooks and articles only want to publish the most classic and typical hemianoptic field loss to avoid confusing the reader. Thus, 'book fields' always and unequivocally respect the vertical meridian, do not drift across the midline, and perfectly localize. 'Real world fields', however, often drift across the vertical midline (especially superiorly in automated perimetry) and patients may have multiple problems simultaneously (e.g., concomitant cataract can cause a diffuse visual field depression or an optic neuropathy can produce a central field defect superimposed on a bitemporal or homonymous field loss). By comparing the nasal to the temporal visual field loss in every case of bilateral deficit a subtle or 'buried' homonymous or bitemporal field defect might be detected.

Recognize that an ‘unreliable’ visual field does not equal a ‘normal’ visual field

An ‘unreliable’ automated or Goldmann visual field is not sufficient documentation of visual field testing in unexplained visual loss. An ‘unreliable’ visual field provides the essentially the same information as no visual field. A confrontation visual field to document the absence of a vertical step is important medically and medicolegally in all patients with ‘unreliable’ visual fields. Careful testing across the vertical meridian can be augmented by using a red test object that might be more sensitive to detection of disease. Some patients (e.g., post-surgical, mentally handicapped, elderly, children) may not be able to perform automated or even Goldmann perimetry and in these cases careful documentation of a good faith effort to test the visual field is important.
Look at the slit lamp biomicroscopy carefully after dilation

Patients with unexplained visual loss may harbor a subtle media opacity that can be easily missed with a cursory view of the anterior segment. Dry and cycloplegic retinoscopy as well as slit lamp biomicroscopy after dilation might demonstrate irregular astigmatism, keratoconus, or an oil droplet, nuclear, or posterior subcapsular cataract.9-10

Remember that a normal appearing macula does not equal a normal functioning macula (e.g., cone dystrophy, other subtle or occult maculopathies)

The retina can look ophthalmoscopically normal or near normal and have markedly poor visual function. The visual acuity may be 20/20 with a ring scotoma and preservation of the foveal sensitivity. Formal visual field testing might disclose a central or cecocentral scotoma in one or both eyes. An enlarged blind spot with a normal appearing optic disc might be seen in patients with peripapillary retinal dysfunction (e.g., multiple evanescent white dot syndrome, acute idiopathic blind spot enlargement syndrome, acute zonal occult outer retinopathy). Symptoms of metamorphopsia and photopsias might suggest retinal disease and the macula should be examined with high magnification and high suspicion. Viewing the details of the macula with a 20 Diopter lens alone is probably not sufficient for detecting subtle abnormalities (e.g., central serous retinopathy, vitreomacular traction, epiretinal membrane, cystoid macular edema, or macular hole).

Non-invasive imaging through the macula (e.g., optical coherence tomography) can also be used to perform an ‘optical biopsy’ of the retina to demonstrate a subtle epiretinal membrane, macular hole, or subretinal fluid. A truly ophthalmoscopically normal macula can be seen in several etiologies (e.g., cone dystrophy, acute zonal occult outer retinopathy, resolved commotio retinae) and these may be detectable only by electrophysiology (e.g., full field or multifocal electroretinography).11-14

Be aware that a normal appearing optic nerve does not equal a normally functioning optic nerve (i.e., retrobulbar optic neuropathy)

A normal appearing optic nerve does not insure normal optic nerve function. In fact, retrobulbar optic neuropathy is common in demyelinating optic neuritis. In these cases, the RAPD may be the only objective sign of an optic neuropathy. In patients who present with a normal appearing optic nerve but clinical evidence for an optic neuropathy (i.e., RAPD, visual acuity or visual field loss, normal structural eye exam) there is a higher likelihood of a compressive etiology than if the optic nerve were atrophic. In an older patient, the presence of optic atrophy might still allow for the possibility of old ischemic optic neuropathy as an etiology. The absence of optic atrophy is not reassuring in the setting of an RAPD and is evidence for a retrobulbar optic neuropathy that demands assessment (e.g., neuroimaging).
Ten easy mistakes to avoid in your next neuro-ophthalmic patient

Table 3. Summary of recommended approach to the evaluation of optic atrophy

1. Obtain a complete history and perform a thorough eye exam to establish an etiology for the optic atrophy (e.g., demyelinating, ischemic, inflammatory, infectious, traumatic, hereditary, congenital, toxic-nutritional) if possible.
2. Review prior records for prior etiology or previous neuroimaging suggesting an etiology for optic atrophy.
3. Cranial and orbital neuroimaging with contrast (i.e., MRI of head and orbit with fat suppression and gadolinium or a CT scan if MRI is contraindicated) for patients with unexplained optic atrophy.
4. Other radiographic (e.g., chest radiography for sarcoid or tuberculosis) and laboratory testing should be considered as directed by the history and exam or the pre-test likelihood (e.g., prevalence in patient population) of specific etiology (e.g., syphilis serology, Lyme titer, sarcoid testing, serum B12 or folate, complete blood count, erythrocyte sedimentation rate).
5. In patients with negative neuroimaging, serial eye evaluations should be performed to verify the stability of the visual loss.
6. Clinicians should consider personally reviewing the neuroimaging with the neuroradiologist in cases of unexplained optic atrophy especially in progressive cases in which a structural lesion is still suspected despite a ‘normal’ imaging report.
7. Consultation with a neuro-ophthalmologist may be indicated for unexplained, non-isolated or progressive optic atrophy.

Recall that optic atrophy is not a diagnosis

Optic atrophy is not an etiologic diagnosis. It is an ophthalmoscopic description of a sign for a possible optic neuropathy.

Evaluate unexplained optic atrophy

Unexplained optic atrophy should be considered to be a compressive optic neuropathy until proven otherwise. In one study, 20% of cases of isolated and unexplained optic atrophy were due to an intracranial lesion. Table 3 lists some recommendations for evaluating optic atrophy.

Summary

In summary, the patient with unexplained visual loss is a common diagnostic dilemma for the ophthalmologist. The clinician should check for an RAPD, perform a formal visual field, compare the nasal and temporal visual fields for a hemianopic vertical step, and should look at the lens and fundus at the slit lamp with high magnification and high suspicion. One should not assume that 20/20 acuity, a normal macula, or a normal optic nerve exclude organic pathology. These simple steps might help the ophthalmologist to avoid making the common errors in evaluating the neuro-ophthalmic patient with unexplained visual loss.
References

Life-threatening diplopia with pupil involvement

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Introduction

The comprehensive ophthalmologist may have to emergently evaluate the patient with diplopia and an abnormal pupil. Three potentially life threatening etiologies will be discussed in this manuscript: 1. Pituitary apoplexy; 2. Mucormycosis; and 3. Aneurysm. Earlier diagnosis and earlier treatment for these conditions makes a difference and prompt neuroimaging is required. A case-based format will be used to illustrate key points in the discussion.

Case 1: Pituitary apoplexy

A 25-year-old female presents with severe (10/10) headache, a right RAPD, a bitemporal hemianopsia, and a third nerve palsy on the right. The patient is the last patient of the day, 4:45 PM, on Friday. What should be done?

An emergent CT-scan, followed by an MRI that night confirmed pituitary apoplexy. The patient underwent successful neurosurgical decompression of a necrotic pituitary adenoma. Pituitary apoplexy may present to the ophthalmologist. Acute and severe headache is often the first symptom but visual loss and diplopia may be the presenting or only features. Hemorrhage or necrosis may occur within a preexisting pituitary macroadenoma and mass effect from expansion into the adjacent cavernous sinus may produce ophthalmoplegia with or without pupil involvement. Medical management of pan-hypopituitarism and prompt surgical decompression may be life or vision-saving.1-5

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Case 2: Mucormycosis

A 35-year-old female with a history of recent diabetic ketoacidosis presented with a complete ophthalmoplegia, a dilated pupil, and an optic neuropathy in the left eye. A CT-scan showed ‘orbital cellulitis and pansinusitis’ and she was treated with antibiotics at an outside hospital but continued to worsen.

The patient underwent otolaryngologic evaluation and sinus surgery showed fungal elements consistent with Mucor. Rhino-orbital-cerebral mucormycosis is associated with a poor prognosis. The diagnosis should be considered in patients with an acute orbital presentation (e.g., proptosis, inflammatory signs) associated with multiple cranial nerve palsies or complete ophthalmoplegia. Concomitant ipsilateral optic neuropathy, or retinal or orbital infarction should increase the suspicion for Mucor. The classic ‘black eschar’ may not be seen. Early local and systemic antifungal treatment and surgical debridement might be life-saving.\(^6\)\(^7\)

Posterior communicating artery aneurysm

The patient with the pupil-involved third nerve palsy is one of highest stakes encounters for the ophthalmologist in clinical practice. Patients with severe headache (i.e., “the worst headache of my life”) or meningeal signs should undergo a non-contrast CT-scan of the head to rule out subarachnoid hemorrhage. Appropriate referral to a neurologist or neurosurgeon for further urgent evaluation and management is critical. Patients with non-isolated third nerve palsies should undergo evaluation and appropriate neuroimaging (i.e., orbital and cranial MRI with contrast along the course of the third cranial nerve and MRA) directed at the topographical localization of the clinical findings (e.g., orbit, superior orbital fissure, cavernous sinus, subarachnoid space, or brainstem).

Although most isolated third nerve palsies in adults are due to ischemia, some of these patients are harboring a life-threatening intracranial aneurysm.\(^8\)\(^3\)\(^3\) Detection of the aneurysm prior to rupture might lead to rapid endovascular coiling or surgical clipping (Fig. 1). Delay in diagnosis and treatment after rupture and subarachnoid hemorrhage is associated with a much worse prognosis.\(^8\)

Classification of isolated third nerve palsy

The isolated third nerve palsy can be classified based upon the degree of involvement of the external muscles (i.e., lid and extraocular muscles of the third nerve) and the internal muscles (i.e., the pupil). A complete external dysfunction third nerve palsy is defined as one that significantly involves all of the external branches of the third nerve (e.g., all of the extraocular muscles innervated by the third nerve and the lid). A third nerve palsy that either does not involve all of the branches of the third nerve (e.g., superior divisional palsy) or does not involve all of the external muscles to a significant degree is considered an incomplete external dysfunction third nerve palsy for the purposes of this discussion. Third nerve palsies with complete external dysfunction may be further subdivided by degree of internal dysfunction (i.e., no internal dysfunction, partial internal dysfunction, or complete internal dysfunction).\(^9\)\(^3\)\(^1\)
Life-threatening diplopia with pupil involvement

Isolated complete external dysfunction third nerve palsy with normal internal function (i.e., "pupil sparing")

A neurologically-isolated third nerve palsy with a completely normal pupil and completely palsied extraocular muscles with complete ptosis is almost never caused by an aneurysm. A single case has been reported due to a basilar artery aneurysm but this is the exception and not the rule. The isolated, complete external dysfunction, 'pupil-spared' (i.e., normal internal function) third nerve palsy is most commonly caused by ischemia (e.g., diabetes). Neuroimaging may be deferred in adults with known vasculopathic risk factors (e.g., diabetes, hypertension) and a neurologically-isolated, complete (external dysfunction) but 'pupil-sparing' third cranial nerve palsy. Other authors have reported finding alternative etiologies for a presumed vasculopathic ocular motor cranial neuropathy on initial neuroimaging however and initial neuroimaging might still be considered.

Isolated incomplete external dysfunction third nerve palsy with no internal dysfunction (i.e., no pupil involvement)

Patients with an isolated incomplete external dysfunction and no internal dysfunction (e.g., divisional palsy) probably should undergo neuroimaging (e.g., MR-scan to rule out a mass lesion and an MRA or CTA). If the MRI and MRA (or CTA) are normal, cerebral angiography should still be considered to investigate the presence of an aneurysm or less likely a carotid cavernous sinus fistula. Although the MRI and MRA (or CTA) combination will usually show an aneurysm large enough to cause a third nerve palsy, cerebral angiography remains the 'gold standard' for the diagnosis of cerebral aneurysms. The combination of an adequately performed and interpreted MRI and MRA (or CTA) may be up to 98% sensitive in the detection of an aneurysm that will bleed. Wong et al. reviewed using CTA as the first line imaging for isolated third nerve palsy presenting without subarachnoid hemorrhage. Nine of 34 (26%) patients had structural lesions as the etiology for the third nerve palsy and five had posterior communicating artery aneurysms. All the aneurysms were detected by CTA. The presence or absence of pain was not of diagnostic value for intracranial aneurysm in this study. They concluded that a 'good quality' CTA was sufficient to detect a compressive aneurysm but that if the CTA results were 'inconclusive' that the patient should undergo catheter angiography.
Table 1. Risk of aneurysm based upon the degree of internal and external dysfunction of the third nerve

<table>
<thead>
<tr>
<th>Third nerve palsy</th>
<th>Complete external dysfunction</th>
<th>Partial external dysfunction</th>
<th>No external dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete internal dysfunction (i.e., pupil involved)</td>
<td>-Pupil-involved third nerve palsy</td>
<td>-Pupil-involved third nerve palsy</td>
<td>-Unlikely to be a third nerve palsy</td>
</tr>
<tr>
<td></td>
<td>-MRI (with MRA or CTA)</td>
<td>-MRI (with MRA or CTA)</td>
<td>-Consider pharmaco-logic dilation, tonic pupil, iris abnormality</td>
</tr>
<tr>
<td></td>
<td>-Highest risk</td>
<td>-Highest risk</td>
<td>-Minimal risk</td>
</tr>
<tr>
<td></td>
<td>-Probably still needs catheter angiogram*</td>
<td>-Probably still needs catheter angiogram*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-MRI (with MRA or CTA)</td>
<td>-MRI (with MRA or CTA)</td>
<td>-Minimal risk</td>
</tr>
<tr>
<td></td>
<td>-Relative pupil sparing third nerve palsy</td>
<td>-Relative pupil sparing third nerve palsy</td>
<td>-Unlikely to be a third nerve palsy</td>
</tr>
<tr>
<td></td>
<td>-MRI (with MRA or CTA)</td>
<td>-MRI (with MRA or CTA)</td>
<td>-Consider pharmaco-logic dilation, tonic pupil, iris abnormality</td>
</tr>
<tr>
<td></td>
<td>-Ill-defined risk</td>
<td>-Ill-defined risk</td>
<td>-Minimal risk</td>
</tr>
<tr>
<td></td>
<td>-May still need catheter angiogram*</td>
<td>-May still need catheter angiogram*</td>
<td></td>
</tr>
<tr>
<td>No internal dysfunction (normal pupil)</td>
<td>-If isolated, complete third nerve palsy with normal pupil (‘pupil sparing’) then can observe vasculopathic patient</td>
<td>-Partial external dysfunction third with normal pupil (no pupil involvement)</td>
<td>-Not applicable</td>
</tr>
<tr>
<td></td>
<td>-Low risk</td>
<td>-Not the same as true ‘pupil-sparing’</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-MRI and MRA (CTA) could be performed</td>
<td>-MRI and MRA (CTA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Catheter angiography if develops pupil involvement</td>
<td>-May still need catheter angiogram*</td>
<td></td>
</tr>
</tbody>
</table>

* Catheter angiography should be considered if the risk of aneurysm is higher than the risk of angiography. Angiography may be deferred if the risk of angiography is higher (e.g., elderly or frail individual with renal failure) than the risk of aneurysm (e.g., child younger than ten years of age). Post-test likelihood of aneurysm can be modified by performing an MRI with MRA or CTA combination.

The clinician must determine in consultation with their local neuroradiologist the sensitivity and specificity of the MRA or CTA technique at their individual institutions. The risk of the angiography must be weighed against the risk of aneurysm in the individual patient.19-23

Isolated incomplete or complete external dysfunction third nerve palsy with partial internal dysfunction (i.e., ‘relative pupil-sparing’ or ‘partial pupil-involvement’)

Isolated partial or relative internal dysfunction or ‘relative pupil-sparing’ third nerve palsy patients should probably undergo MRI and MRA (or CTA). Although
Life-threatening diplopia with pupil involvement

This presentation is often due to ischemia, a compressive lesion including aneurysm remains in the differential diagnosis.\textsuperscript{24-27} Cullom \textit{et al.} reviewed ten ‘relative pupil-sparing’ third nerve palsies and none had an aneurysm.\textsuperscript{24} On the other hand, in another study of 24 isolated ‘relative pupil-sparing’ third nerve palsies, ten had a tumor or aneurysm.\textsuperscript{26} As above, cerebral angiography may still be needed if the MRI and MRA (or CTA) are negative because of the small but real possibility of a cerebral aneurysm. There is insufficient evidence in the literature to recommend reliance on the MRI with MRA (or CTA) alone in this setting. Chou \textit{et al.} reported that among 25 patients with presumed microvascular third nerve palsy, seven (28\%) had some degree of pupil involvement and three of these seven (43\%) had greater than 2 mm of anisocoria.\textsuperscript{17}

\textit{Isolated complete or incomplete external dysfunction, but complete internal dysfunction (‘the pupil-involved third nerve palsy’)}

Complete internal dysfunction (\textit{i.e.}, ‘pupil involvement’) is a sign of a compressive lesion such as aneurysm. An initial MRI and MRA (or CTA) combination should be performed to rule out non-aneurysmsal etiologies for third nerve palsy but even if the study is negative, a cerebral angiogram should still be strongly considered for the ‘pupil involved’ third nerve palsy.\textsuperscript{28-32} The decision to proceed or not to proceed with catheter angiography in this setting should be determined on an individual basis. The clinician needs to weigh the risk of aneurysm and the risk of angiography in the decision making process.

\textbf{Summary}

In summary, diplopia with pupil involvement can be a sign of life-threatening disease of the cavernous sinus or orbital apex (\textit{e.g.}, pituitary apoplexy or Mucormycosis). The clinician should be aware that the patient with an isolated third nerve palsy may be harboring an intracranial aneurysm. The degree of completeness of external dysfunction and internal dysfunction (pupil involvement) should drive the decision making. If the risk of aneurysm is low (\textit{e.g.}, isolated presumed vasculopathic ‘pupil-spared’ complete third nerve palsy) or the risk of angiography is high (\textit{e.g.}, elderly patient with high risk of renal failure or risk of stroke), then an MRI and MRA (or CTA) combination is a reasonable screening study. In patients with a moderate or uncertain risk of aneurysm (\textit{e.g.}, partial external dysfunction or partial internal dysfunction third nerve palsy), MRI and MRA (or CTA) combination may not be sufficient to exclude aneurysm. The clinician should consult with their neuroradiologist regarding their respective institution’s MRA or CTA and which might be better screening study locally (\textit{i.e.}, institutional experience with one technique or another, quality of the technology, and availability of the study). Although cranial contrast MRI is superior to CT for the evaluation of the third nerve (\textit{e.g.}, enhancement of the third nerve, cavernous sinus) one individual institution’s CTA may be better than their MRA or vice versa. In some cases therefore a MRI with MRA followed by CTA might be necessary. In high-risk cases for aneurysm (\textit{i.e.}, ‘pupil involved third nerve palsy’), catheter angiography may still be required despite a negative MRI and MRA (or CTA) combination.

\textbf{References}

Life-threatening diplopia with pupil involvement

Optic neuritis: What’s hot and what’s not…

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**Introduction**

Optic neuritis (ON) is a common cause of acute visual loss in adults. ON in this manuscript refers to idiopathic or demyelinating optic neuropathy. This paper provides an update on the diagnosis, evaluation and management, treatment and prognosis of ON in adults. Recent clinical trials and new developments in the treatment of multiple sclerosis are emphasized. The ‘typical’ clinical profile for ON is contrasted with the atypical presentations in Table 1.\(^\text{1-11}\)

**Table 1. Features of typical versus atypical optic neuritis in adults**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Typical</th>
<th>Atypical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>Age</td>
<td>Young adult</td>
<td>Older patient</td>
</tr>
<tr>
<td>Laterality</td>
<td>Unilateral</td>
<td>Bilateral simultaneously or rapidly sequential</td>
</tr>
<tr>
<td>Pain</td>
<td>With eye movement</td>
<td>Painless or pain out of proportion to findings</td>
</tr>
<tr>
<td>Optic disc</td>
<td>Retrobulbar (65%)</td>
<td>Severe disc edema</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Few (if any)</td>
<td>Marked hemorrhages 360 degrees</td>
</tr>
<tr>
<td>Exudates</td>
<td>Uncommon</td>
<td>May see macular star figure in neuroretinitis</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Rare</td>
<td>Suggests inflammatory disease</td>
</tr>
<tr>
<td>Course</td>
<td>Improves</td>
<td>Lack of improvement or progression</td>
</tr>
</tbody>
</table>

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*edited by Jonathan D. Nussdorff*  
The Optic Neuritis Treatment Trial

The Optic Neuritis Treatment Trial (ONTT) was a multicenter, randomized, placebo-controlled clinical trial of oral and intravenous (IV) corticosteroid therapy for ON. Patients were aged 18 to 46 years and had an ipsilateral optic neuropathy. Patients were excluded if they had previous ON, prior corticosteroid treatment for ON or MS, or systemic diseases other than MS that might be the cause for ON. There were three treatment arms: 1. IV methylprednisolone 250 mg every six hours for three days followed by oral prednisone (1mg/kg per day for 11 days and a short taper); 2. oral prednisone alone (1 mg/kg per day for 14 days followed by a short oral taper); and 3. oral placebo for 14 days. In the ONTT, all patients had a brain MR scan, serum antinuclear antibody (ANA) for systemic lupus erythematosus, serologic testing for syphilis (e.g., FTA-ABS), and a chest radiograph for sarcoidosis. None of the laboratory testing was helpful in the diagnosis of typical ON. A lumbar puncture in the ONTT was optional but only disclosed changes consistent with demyelinating disease when positive. The ONTT recommendations are that chest radiograph, laboratory tests, and lumbar puncture are unnecessary for typical ON. Brain MR imaging however is a very useful test for ON and provides the strongest prognostic information for MS in patients with ON. Fluid attenuation inversion recovery (FLAIR) sequences may increase the sensitivity for the detection of periventricular white matter lesions on cranial MRI (Fig. 1). Orbital imaging with fat suppression and gadolinium in addition to the brain MR may be useful in ON.

Fig. 1. Axial T2-weighted magnetic resonance imaging with fluid attenuation inversion recovery (FLAIR) shows multiple periventricular white matter lesions consistent with the clinical diagnosis of multiple sclerosis.
Optic neuritis: What’s hot and what’s not …

Visual outcome in ONTT

In the ONTT, although IV steroid sped the rate of recovery, all three treatment arms had good final visual acuity and visual field outcomes. Visual acuity at one year was ≥ 20/40 in 95% of the placebo group, 94% of the IV steroid group, and 91% of the oral prednisone group. In the > 10 year analysis, visual acuity was ≥ 20/20 in 74%; from 20/25 to 20/40 in 18%; from 20/40 to 20/200 in 5%; and < 20/200 in only 3%. Recurrent ON in either eye occurred in 35% and was more frequent in MS (P <.001).\(^1\)

Treatment of optic neuritis

The ONTT conclusions regarding treatment of ON were as follows: 1. High-dose IV followed by oral corticosteroids sped the rate of visual recovery but did not affect final visual outcome; 2. oral prednisone at conventional doses not only did not improve visual outcome but increased the rate of new attacks of ON and they are probably not indicated; and 3. IV followed by oral corticosteroids reduced the rate of clinically definite MS during the first two years although this effect subsided by three years.\(^1\)

What treatments are available for multiple sclerosis?

Ophthalmologists should be aware that several recent trials have demonstrated the efficacy of new immunomodulatory treatments for MS. For example, the Controlled High-Risk Subject Avonex® Multiple Sclerosis Prevention Study (CHAMPS) was a randomized, double-masked, placebo-controlled, clinical trial (n = 383) of IFN beta 1-a (Avonex®). All patients had an acute first attack of a clinical demyelinating event (e.g., optic neuritis, incomplete transverse myelitis, or brainstem or cerebellar syndrome) and MR demyelinating lesions (i.e., ≥ 2 high signal white matter abnormalities on T2-weighted images). All patients received IV methylprednisolone and then were randomized to either weekly intramuscular (IM) IFN beta-1a (n = 193) or placebo (n = 190).\(^2\) There was a 44% reduction in the development of clinically definite MS in the treatment group compared to controls. The IFN treated group also had a relative reduction in the volume of brain lesions (p < 0.001); fewer new or enlarging lesions (p < 0.001); and fewer gadolinium-enhancing lesions (p < 0.001) on cranial MR.\(^2\)

In another study, the Early Treatment of Multiple Sclerosis (ETOMS) trial, 41 (31%) of 131 patients on interferon beta-1a compared with 62 (47%) of 132 on placebo developed clinically definite MS. The authors concluded that early treatment with interferon beta-1a was effective in reducing conversion to MS and in slowing progressive loss of brain tissue on MR in patients with clinically isolated syndromes (e.g., optic neuritis). In other studies, interferon beta-1a and beta 1-b have shown similar effects for the treatment of MS.\(^2\)

Although the risk for MS is lower for patients with a normal initial MR scan after monosymptomatic ON, these patients still have a 16% chance of developing MS at year five. A repeat cranial MR scan (in six months to one year) might be
considered in these patients to detect new MR lesions over time. In the long-term follow-up of the ONTT cohort there were 108 patients who had not developed clinically definite MS ten to 14 years after enrollment. At least one T2 white matter lesion (≥ 3 mm) was seen on follow-up MR scan in 27 (44%) of 61 patients with a normal baseline MRI. On the other hand, new MR lesions (≥ 3 mm) were present in 26 (74%) of 35 patients with an abnormal baseline MR scan. This suggests that there are patients who present with monosymptomatic ON who have no clinical signs or MR evidence of demyelination after more than ten years of follow up. In this same ONTT cohort there were 127 patients with clinically definite MS. Functional Systems Scale and Expanded Disability Status Scale (EDSS) were performed and the disability of most patients was mild (65% had EDSS score < 3.0). The degree of disability was unrelated to baseline MR scan findings. The conclusion was that many patients who develop clinically definite MS following ON have a relatively benign course for at least 10 years. The decision for and the timing of serial MR scans and consideration for MS treatment should therefore be coordinated with a local neurologist on a case by case basis.

Summary

Ophthalmologists evaluating patients with an acute demyelinating attack of ON should be aware of the results of the ONTT. Although typical ON does not require any laboratory testing or a lumbar puncture, atypical cases may require additional testing. An MR scan of the brain should be considered in all cases of ON and the MR scan provides powerful prognostic information regarding MS that should guide decision making for treatment or referral to a neurologist. Although IV steroids speed the rate of visual recovery in ON they do not affect final visual outcome. Oral steroids in conventional doses should probably not be given for typical ON. New therapies with immunomodulatory therapy (e.g., interferon beta therapy) may reduce the rate of MS even after monosymptomatic demyelinating attacks and the ophthalmologist should coordinate the care of these patients on an individualized basis with a neurologist.

References

Optic neuritis: What’s hot and what’s not ...

What to tell your next patient with non-arteritic anterior ischemic optic neuropathy (NAION) ... other than “nothing can be done”

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Introduction

Non-arteritic anterior ischemic optic neuropathy (NAION) is a common cause for visual loss in adults but the precise etiology remains elusive and is likely multifactorial. This chapter will review several hypotheses regarding the pathogenesis of NAION; will discuss some preventive measures that might decrease the chance of fellow eye involvement; will summarize the current status of treatment; and will make some recommendations for counseling patients with NAION. The author emphasizes however, that the pathogenesis and etiology of NAION remain controversial and that the recommendations of this article reflect the author’s opinions, experience and current practice and should not be construed as a ‘standard of care’.

Case

A 60-year-old man presented with acute painless loss of vision OD. Past medical history was significant for poorly controlled hypertension (blood pressure of 200/80) and variably controlled diabetes mellitus (blood sugars in 300 mg/dL and hemoglobin A1C of 10), elevated cholesterol, and coronary artery disease. The patient had a 40-pack-year smoking history and drank three glasses of wine each evening before bed. Medications included oral atenolol at night, insulin, and atorvastatin. He occasionally used sildenafil and took a sleeping pill at night on a periodic basis. He had daytime sleepiness and the wife stated that he snored loudly. The visual acuity was 20/200 OD and 20/20 OS. There was a right relative afferent pupillary defect. Visual field testing was normal OS but showed an inferior altitu...
dinal defect OD. Ophthalmoscopy showed a small cup to disc ratio and a few disc drusen OS. The right optic nerve showed optic disc edema with a few peripapillary hemorrhages (Fig. 1). Serum erythrocyte sedimentation rate and C-reactive protein were normal. There was no headache, scalp tenderness, or jaw claudication. The patient was diagnosed with NAION and was told: “You have had a stroke in your optic nerve, there is no treatment, and nothing can be done.” The patient left depressed and with a feeling of hopelessness.

What causes non-arteritic ischemic optic neuropathy?

The cause for NAION is unknown. Several vasculopathic risk factors have been implicated but no single factor is likely to be sufficient or necessary for the disorder.1-12 Table 1 lists a number of proposed associated factors in NAION.

What is the evaluation for NAION?

The ophthalmologist should consider contacting the patient’s primary care physician to diagnose, evaluate, and possibly treat any underlying vasculopathic risk factors (e.g., hypertension, diabetes, atherosclerosis, high cholesterol). Smoking cessation should be strongly encouraged.11 Although the evidence for aspirin use to prevent fellow eye involvement in NAION is conflicting, patients with specific
What to tell your next patient with NAION

Table 1. Some proposed risk factors for NAION (courtesy of Robert Sergott, MD)

- Hypertension or Hypotension (nocturnal, iatrogenic, or post-surgical)
- Hyperglycemia (Diabetes mellitus)
- Hyperlipidemia (hypercholesterolemia)
- Hyperhomocysteinemia
- Hypoxia (e.g., smoking)
- Hypoperfusion (e.g., fluid overload, atherosclerosis, rarely embolic)
- Hematocrit low (e.g., anemia, severe blood loss)
- Hypersomnia (obstructive sleep apnea)
- High intraocular pressure (? role in post cataract surgery NAION)

Table 2. Selected medications that might cause or worsen hypotension

- Anti-hypertensives (e.g., beta blockers, calcium channel blockers)
- Diuretics (e.g., furosemide, acetazolamide, hydrochlorothiazide)
- MAO inhibitors (e.g., isocarboxazid, phenelzine, tranylcypromine for depression)
- Tricyclics (e.g., amitriptyline)
- Phenothiazines (e.g., thioridazine)
- Vasodilators (e.g., nitrates, hydralazine)
- Alpha-blockers (e.g., doxazosin, terazosin, tamsulosin)
- Sedatives (e.g., barbiturates, opiates)
- Other medications (e.g., quinidine, levodopa, vincristine, sildenifil)

Vasculopathic risk factors might benefit from anti-platelet therapy to reduce the risk of myocardial infarction. Aspirin therapy however has no apparent effect on visual outcome in NAION. A small cup to disc ratio has been proposed as a structural risk factor for NAION. Patients with no other vasculopathic risk factors, especially young patients, might have underlying optic disc drusen (and a crowded and small optic disc). Ocular ultrasound for buried disc drusen might be useful in establishing a risk factor for NAION in such patients. Obstructive sleep apnea might be an additional treatable risk factor and the clinician might inquire about snoring and excessive daytime sleepiness, especially in obese middle aged males.

Nocturnal alcohol use, bed-time dosing of anti-hypertensives, and other medications at night (including topical beta blockers, sedative, and sildenifil) might also be related to NAION. Table 2 lists potential medications that might cause hypotension and overaggressive treatment of hypertension should be avoided. Appropriate consultation with the primary care physician is advised before altering the medication regimen of the patient, however.

Although the precise etiology of NAION is unknown, embolic and hypercoaguable state are rare causes. In typical NAION, no hypercoaguable state work up is indicated. Likewise, cardiac echo and carotid Doppler are not necessary. Patients with a visible embolus, involvement of multiple circulations (e.g., choroidal or retinal artery occlusion or cotton wool patches), or prior transient visual loss episodes preceding the AION might benefit from more aggressive thrombotic and embolic evaluation however. Anti-phospholipid antibody and plasma homocysteine have been implicated in NAION especially in young patients without vasculopathic risk factors or with recurrent disease but there is insufficient evidence to
make a firm evidence-based recommendation on the diagnostic yield for these tests especially for typical NAION.\textsuperscript{21-27}

Neuroimaging studies are not necessary in typical unilateral NAION. Patients with atypical features including progressive visual loss, optic atrophy at presentation, or persistent optic disc edema (> 2 months) might benefit from magnetic resonance imaging of the head and orbit with gadolinium and fat suppression to exclude a compressive etiology (e.g., optic nerve sheath meningioma).

Role of the ophthalmologist

The most important priority for the ophthalmologist dealing with AION is to exclude giant cell arteritis (e.g., laboratory testing, temporal artery biopsy, corticosteroids as necessary).\textsuperscript{28} The roles of the ophthalmologist in NAION should be to reassure the patients; to educate them on the treatable vasculopathic, lifestyle, and pharmaceutical risk factors, and to give hope to the patient. Typical NAION usually remains static or slightly improves over time once the disc edema phase resolves. The incidence of fellow eye involvement in NAION was 14.7\% in the ischemic optic neuropathy decompression trial (IONDT) cohort over 5 years.\textsuperscript{29} Patients should be told that once the disc edema resolves NAION is unlikely to recur in the same eye (6\%) and that NAION is not typically a progressive or blinding disorder once the optic disc edema subsides.

Physicians should avoid telling the patient that “nothing can be done” as it is not helpful to the patient and probably not true. Patients with visual loss may suffer a grief reaction, depression and feelings of hopelessness that might respond to simple counseling regarding the natural history of NAION. Patients with bilateral AION may benefit from low vision services.

What are the treatments for NAION?

Although many interventions have been tried (e.g., anticoagulants and antiplatelet agents, diphenylhydantoin, levodopa, and hyperbaric oxygen), there remains no proven effective and widely accepted therapy in NAION.\textsuperscript{30-42} The major recommendation for NAION is to evaluate and treat any underlying risk factors and reduce the risk to the fellow eye. This should be done in coordination with the patient’s primary care physician.

Topical brimonidine and memantine have been purported to have neuroprotective properties in animals but any effect in NAION would be strictly theoretical and is completely unproven in humans. Corticosteroids have been the mainstay of treatment for arteritic ION but are unproven in NAION. Levodopa is a controversial therapy in NAION. The published studies showed some positive effect for levodopa on visual acuity in NAION but the studies were compromised by small sample sizes and significant statistical and methodologic concerns.\textsuperscript{37-40} Optic nerve decompression was shown in a randomized trial to be ineffective, may in fact be harmful, and has largely been abandoned.\textsuperscript{41-42} Other surgical procedures have been proposed (e.g., transvitreal optic neurotomy) but remain unproven and have weak biological rationale for efficacy.
What to tell your next patient with NAION

Summary

In summary, the diagnosis of NAION is a clinical one. The major responsibility of the ophthalmologist is to exclude giant cell arteritis (i.e., arteritic AION). The evaluation and management should be directed to the underlying vasculopathic risk factors. Smoking cessation should be encouraged. Patients might consider discontinuing exacerbating factors for nocturnal hypotension (e.g., nocturnal alcohol use, nocturnal sedative or antihypertensive use). Aspirin therapy might be useful for reduction of myocardial infarction risk in at-risk patients. To date, there is no proven effective and widely accepted therapy for NAION. Patients should be counseled regarding the natural history of the disorder, the risk to the fellow eye, and provided with low vision services as needed.

References

MRI and CT: Which is which, why to order, and when

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Introduction

Neuroimaging has evolved tremendously over the last few decades and has changed the evaluation of neuro-ophthalmic conditions. This manuscript provides an overview of orbital and intracranial imaging (e.g., conventional computed tomography (CT) and magnetic resonance (MR) scanning); will review two special sequences (i.e., fat suppression and fluid attenuation inversion recovery); and will summarize recommendations for imaging in neuro-ophthalmology.

Computed Tomography (CT) versus Magnetic Resonance Imaging (MRI): Which is which?

Orbital and cranial CT- and MR-scans are the mainstays of neuroimaging for the ophthalmologist. The technique of CT-scanning (introduced in 1972) is based upon x-rays. In a conventional x-ray (e.g., skull film), there is attenuation of the x-ray by tissues of various densities. Denser tissue (e.g., bone) will block the exiting x-rays and the image on the film is by convention ‘bright’. Thus, lesions on CT-scan can be described as hyperdense, isodense, or hypodense. The computer reformats the x-ray information into the CT image (Fig. 1). The advantages of CT-scanning are listed in Table 1.

MR imaging as opposed to CT employs no x-rays and instead MRI is based upon detection of the interaction of protons (mostly hydrogen within water in your body) within a powerful magnetic field. The protons of the body, mostly in water, align within the magnetic field. A radiofrequency pulse is applied and then turned off. The protons move from a higher energy level to a lower energy level and the signal produced can be imaged as signal intensity. Thus, as opposed to density in CT-scans, lesions on MRI are typically described as hyperintense.
Fig. 1. Axial orbital computed tomography (CT) scan. Notice very dense bone is bright on CT.

Table 1. Advantages of computed tomography (CT) scan

- Widespread availability in most hospitals
- Easy to perform for patient and technician
- Relatively inexpensive
- Rapid test time

Isointense, or hypointense. Bone contains few mobile protons (little water) and appears hypointense on MRI and therefore CT is the superior study for bone detail. Details regarding the physics of MRI are beyond the scope of this manuscript. MR studies can be ‘weighted’ towards T1 (the ‘anatomy’ study) or T2 (the ‘pathology’ study). Fat is typically bright on T1 (Fig. 2) and cerebrospinal fluid is dark on T1 and bright on T2 (Fig. 3). The ophthalmologist does not have to order a T1- and T2-weighted study because these sequences are routine.1-6

Should I order contrast material?

Contrast in CT- and MR-scanning improves sensitivity and specificity and should be strongly considered for most neuro-ophthalmic indications unless contraindicated. The contrast material in CT is iodinated and contrast allergy and renal failure are relative contraindications to contrast CT. Thyroid eye disease typically only requires a non-contrast CT as iodinated contrast may affect the treatment of systemic thyroid disease. Likewise patients who require localization of an intraocular or intraorbital foreign body do not often require contrast material. Patients with hydrocephalus who are undergoing a CT to judge increase or decrease in ventriculomegaly also do not require contrast material. The contrast material for MR is
MRI and CT: Which is which, why to order, and when

Fig. 2. Axial T1-weighted, non-fat suppressed, pre-contrast, magnetic resonance (MR) imaging shows bright fat in the orbit.

Fig. 3. T2-weighted MRI showing bright cerebrospinal fluid within the ventricles. A few periventricular white matter lesions can be seen in this patient with optic neuritis.

A paramagnetic material called gadolinium and it is not iodinated like CT contrast material. Gadolinium should be ordered in virtually all MR-scans in neuro-ophthalmology. Gadolinium is very safe, rarely produces allergic reactions, and does not cross-react with either iodinated CT contrast or fluorescein dye. Gadolinium for MR is also the contrast of choice for patients with renal insufficiency.
When to order a CT- versus an MR-scan?

MRI is far superior to CT for most neuro-ophthalmic conditions. CT-scan is not as sensitive as MR for soft tissue pathology and does not image the cavernous sinus, posterior fossa, and meningeal pathology as well as MR. CT is better than MR, however, for bone disease (e.g., trauma/fracture, hyperostosis, sphenoid wing agenesis in neurofibromatosis-1, craniosynostosis, paranasal sinus disease, clival or skull base pathology, bone destruction or bony erosion); calcification (e.g., optic nerve head drusen, meningioma, craniopharyngioma, retinoblastoma); or acute intracranial hemorrhage (e.g., subarachnoid hemorrhage, pituitary apoplexy, vascular malformation, intracranial hematoma). A CT-scan is also faster than an MR-scan and should be used in emergent situations (e.g., acute stroke, brain abscess, pituitary apoplexy, intracranial shunt malfunction and hydrocephalus). CT may be necessary for cases with contraindications to MR-scan (e.g., severe claustrophobia, cochlear implant, ferromagnetic aneurysm clip, pacemaker, or metallic foreign body). Table 2 lists the indications for CT-scan. Table 3 lists the indications for MRI.8-17

Table 2. Indications for a CT-scan

- Acute hemorrhage (e.g., subarachnoid hemorrhage, hemorrhagic stroke, pituitary apoplexy)
- Acute trauma (e.g., orbital fracture, traumatic optic neuropathy)
- Brain abscess (i.e., emergent scan)
- Bone disease
- Calcifications (e.g., optic nerve head drusen, calcification in retinoblastoma, meningioma, or craniopharyngioma, hyperostosis of bone)
- Orbital cellulitis or sinus disease
- Contraindication to MRI (e.g., pacemaker, claustrophobia, metallic foreign body)
- Urgent or emergent study needed

Table 3. Indications for MR imaging

<table>
<thead>
<tr>
<th>Condition</th>
<th>Imaging Protocol</th>
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<tbody>
<tr>
<td>Papilledema</td>
<td>Contrast head MR and MR venography (exclude sinus thrombosis)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>MR head and orbit with gadolinium, FLAIR, and fat suppression</td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>MR head and orbit with gadolinium, FLAIR, and fat suppression</td>
</tr>
<tr>
<td>Chiasmal lesion</td>
<td>MR head with contrast and FLAIR (sella sequence)</td>
</tr>
<tr>
<td>Retrochiasmal lesion</td>
<td>MR head with contrast and FLAIR (diffusion for stroke)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>MR head with contrast (localize nystagmus)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>MR head with contrast</td>
</tr>
<tr>
<td>Supranuclear palsy</td>
<td>MR head with contrast (brainstem)</td>
</tr>
<tr>
<td>Nuclear palsy</td>
<td>MR head with contrast (brainstem)</td>
</tr>
<tr>
<td>Internuclear ophthalmoplegia</td>
<td>MR head with contrast (brainstem)</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>MR head/orbit with contrast (follow nerve)</td>
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<tr>
<td>Horner syndrome: Localize lesion pharmacologically</td>
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<tr>
<td>Preganglionic</td>
<td>MR head with contrast and MR/MRA neck to T2 in chest</td>
</tr>
<tr>
<td>Postganglionic</td>
<td>MR head with contrast above superior cervical ganglion</td>
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</table>
MRI and CT: Which is which, why to order, and when

Should I order head or orbit study?

The clinician should direct the imaging study to the topographical localization of the problem by the clinical history and physical exam. Orbital CT imaging is different from cranial imaging because it may be angled differently or use thinner scan slices (e.g., 3 mm versus 5 mm CT). In addition, when the film or digital image displays a magnified orbital image, the posterior part of the brain including the occipital lobe is often not displayed (Fig. 4). The clinician should order a head study if the localization of the clinical findings implicates a brain lesion. In a patient with a homonymous hemianopsia the head study is the necessary study rather than the orbit. An orbital study should be performed if the lesion is intraorbital (e.g., orbital inflammatory pseudotumor or thyroid ophthalmopathy). If the lesion is potentially involving the orbit and the head (e.g., optic neuropathy, ocular motor cranial neuropathy) then a head and orbit study should be performed. The ophthalmologist should specify on the radiographic order form the precise topographical localization (‘where is the lesion’) of the problem in order to assist the radiologist in interpreting the films. I would recommend strongly against simply listing ‘diplopia’ or ‘visual loss’ as the indication for the imaging study as this vague information does not provide localizing data to the neuroradiologist.

Do I need to specify the plane of imaging?

Orbital and cranial studies can provide images in multiple planes (e.g., axial, coronal, and sagittal). The most commonly performed views in CT-scanning are axial
and coronal, but sagittal views can be obtained either directly or with computer reconstruction. Reconstructed views may be the only option in a patient who is unable to extend or flex the neck for a direct view. New software permits high quality reconstructed views that can be comparable to direct CT views. Midline lesions (e.g., pituitary adenoma) are sometimes better imaged with coronal section and certain neuro-ophthalmic pathology can be better seen with different planes of imaging (e.g., sagittal imaging for the Chiari I malformation).

**Special sequences in MRI**

There are two special sequences for neuro-ophthalmology that deserve mention: fat suppression and fluid attenuation inversion recovery (FLAIR). Normal fat gives very bright signal intensity on T1-weighted MR-scans. Special software can suppress the normal bright signal of fat (Fig. 5) on T1 (‘fat suppression’). Likewise, CSF is very bright on T2-weighted MR images. The CSF can be suppressed using fluid attenuation inversion recovery (FLAIR). FLAIR (Fig. 6) sequences allow visualization of underlying pathology (e.g., white matter demyelination, posterior reversible encephalopathy) that might be obscured by the bright signal of normal cerebrospinal fluid. Likewise, fat suppression (Fig. 7) allows visualization of abnormal bright signal on T1 without obscuration from the normal fat signal. Fat suppression should be ordered in orbital MR-scans in order to allow any pathologic contrast enhancement to be seen.

![Axial T1-weighted post contrast fat suppressed images show normal enhancement of the extraocular muscles in the orbit.](image-url)
**Fig. 6.** Fluid attenuation inversion recovery sequence. Axial brain T2 weighted MRI with fluid attenuation inversion recovery (FLAIR) shows periventricular white matter lesions. The normal bright cerebrospinal fluid signal is suppressed on FLAIR.

**Fig. 7.** There is enhancement and enlargement of the right optic nerve sheath on this T1-weighted fat suppressed MR image. The normal bright fat signal on T1-weighted imaging is suppressed using fat suppression.

**Table 4.** Stepwise approach to ordering imaging studies in ophthalmology

- Choose CT or MR imaging. (In general, MR-scan is superior to CT). Look at specific CT indications before choosing CT over MR (see Table 2).
- Order contrast material unless contraindicated or not needed.
- Localize the lesion clinically and order the appropriate imaging location (e.g., head, orbit, both). Fill out the radiographic requisition form personally with sufficient clinical detail and localizing information (‘where is the lesion’) to allow the neuroradiologist to appropriately interpret the imaging study.
- Order specialized sequences as needed (e.g., fat suppression for orbital MR imaging with contrast and FLAIR for white matter lesions).
- Provide the radiologist with explicit information on the ordering form regarding localization (‘where is the lesion’) and the differential diagnosis (‘what is the lesion’).
- If the imaging report is ‘normal’ but the clinical findings strongly suggest a structural lesion (e.g., homonymous or bitemporal hemianopsia, progressive optic neuropathy or ocular motor cranial neuropathy) then the ophthalmologist should consider calling the radiologist to insure that the study was correctly performed and adequately imaged the area of interest; personally reviewing the films with the neuroradiologist, consulting neuro-ophthalmology, or repeating the neuroimaging study with special attention to the topographical localization based on the clinical findings.

**Summary**

Although there are some exceptions, MR-scanning is superior to CT-scanning for most neuro-ophthalmic indications. Contrast material should almost always be included in the study unless there is a specific contraindication. Special sequences such as fat suppression and FLAIR improve diagnostic accuracy in MR. Precise localization information (‘where is the lesion’) and the
differential diagnosis (‘what is the lesion’) should be provided explicitly to the radiologist in order to improve the interpretation of the film. If the imaging report is ‘normal’, but clinically the patient should have a structural lesion then the ophthalmologist should consider reviewing the film personally with the radiologist, consulting a neuro-ophthalmologist, or repeating the neuroimaging study. Most of the errors in neuroimaging can be avoided by more direct and explicit communication between the ophthalmologist and the neuroradiologist.21

References

Optical Coherence Tomography (OCT) in neuro-ophthalmology

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Introduction

Optical coherence tomography (OCT) is a non-invasive, non-contact, trans-pupillary imaging method with excellent in vivo resolution (10 to 17 microns). OCT provides cross-sectional images using the principles of optical back-scattering of light. The retinal nerve fiber layer (RNFL) thickness can be measured by determining the depth difference between the defined inner border of retinal nerve fiber layer and the internal limiting membrane. The optic nerve RNFL is measured in the peripapillary retina at 256 points and grouped into 12 clock-hour sectors. The patient’s RNFL is plotted within a color-coded normative data graph.1-2

In addition, optical sectioning through the macula with the OCT can provide a cross-sectional image through the retina that might demonstrate subtle or even non-ophthalmoscopically visible macular pathology.

This paper will review the author’s uses of OCT in neuro-ophthalmology, including: 1. assessing patients with unexplained visual loss by differentiating macular from optic nerve pathology; 2. following change over time in RNFL thickness in patients with various optic neuropathies; 3. determining if patients with apparent or suspected abnormalities seen with the ophthalmoscope (e.g., glaucoma suspect, physiologic versus real optic disc pallor, papilledema versus pseudopapilledema) have any corresponding structural RNFL change (i.e., thinning or thickening); 4. providing prognostic information to patients with compressive optic neuropathy based upon RNFL loss or preservation.

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Assessment of unexplained visual loss (Is it retina or optic nerve?)

Case one

A 55-year-old diabetic male presents with unexplained visual loss in the right eye. Visual acuity is 20/50 OD and 20/20 OS. He has a history of non-proliferative diabetic retinopathy OU. Both pupils are very sluggishly reactive and there is light-near dissociation of the pupils secondary to diabetic autonomic neuropathy. No relative afferent pupillary defect was detected but both pupils had poor light reaction. Formal visual field testing reveals a small relative central scotoma OD and non-specific constriction OS. The fundus exam shows scattered dot and blot hemorrhages OU but the optic nerve appears normal. Is it retina or optic nerve?

Unexplained visual loss is a common presenting complaint to the comprehensive ophthalmologist. If the pupil, anterior segment, and refraction exams are non-diagnostic, then the clinician is challenged to differentiate a potential optic neuropathy from a maculopathy as the etiology for the visual loss. Subtle findings in the macula can easily be missed, even with careful scrutiny of the retina with high magnification and high suspicion. The OCT has the ability to provide an ‘optical biopsy’ of the macula and can provide resolution that complements or exceeds the clinical ophthalmoscopic findings. The OCT can be used in conjunction with or sometimes in place of the traditional retinal imaging techniques such as fluorescein angiography or fundus photography. In our experience, the most commonly missed macular causes for unexplained visual loss are: 1. small macular hole (Fig. 1); 2. subtle epiretinal membrane (Fig. 2); 3. diffuse macular edema (Fig. 3), shallow subretinal fluid (Fig. 4); 4. vitreomacular traction (Fig. 5), occult subretinal neovascular membrane, or juxtafoveal telangiectasias (Fig. 6). In the case above, the OCT showed macular edema (Fig. 3) from diabetes as the cause for the loss of central vision and field.

The OCT has been very helpful in differentiating these subtle macular lesions and allows me to make more appropriate directed referrals to our medical retina specialist, rather than simply asking the retina consultant to ‘screen’ all of our unexplained visual loss patients for underlying maculopathy. Conversely, in patients with a completely normal macula ophthalmoscopically and a normal OCT through the macula, I can concentrate my efforts on excluding an optic neuropathy or other etiology as the cause of the visual loss.

In addition, there are circumstances when patients have both optic nerve and macular pathology. In these circumstances, it might be useful to know if there is fluid under the retina causing the visual loss. Some examples include optic disc edema with macular star figure, papilledema with subretinal fluid, or an optic pit with a serous retinal detachment. In patients with papilledema (e.g., pseudotumor cerebri), decreased acuity is often a late and bad prognostic sign and in the acute or chronic setting may be an indication for surgery (e.g., optic nerve sheath fenestration). If, however, the visual acuity loss is due to subretinal fluid and not the optic neuropathy per se, this might be an indication for continued observation and medical treatment rather than surgery. OCT may show the extent of subretinal fluid under the macula and help the clinician determine if the visual loss is macular or optic nerve in origin.
Fig. 1. Macular OCT showing defect in retina corresponding to a macular hole.

Fig. 2. Macular OCT shows thickening corresponding to an epiretinal membrane.

Fig. 3. Macular OCT shows thickening corresponding to macular edema with cystic spaces.
Fig. 4. Macular OCT shows subretinal fluid under the retina (arrow).

Fig. 5. Macular OCT shows vitreomacular traction (arrow).

Fig. 6. Macular OCT shows juxtafoveal telangiectasia (arrow).
Optical Coherence Tomography (OCT) in neuro-ophthalmology

Following change over time in the retinal nerve fiber layer thickness in optic neuropathies

The traditional means for following improvement or worsening in patients with an optic neuropathy includes assessment of the visual acuity, formal visual field testing, measurement of the relative afferent pupillary defect if present, and ophthalmoscopic and photographic evaluation of the optic disc. OCT of the peripapillary RNFL might provide additional information for the clinician.10-15

In optic neuritis, the patient typically improves over time clinically and in anterior ischemic optic neuropathy there is usually a static course once the disc edema phase resolves. Documentation of stability or change in the RNFL in patients with an optic neuropathy might be helpful in confirming the diagnosis and for prognostic purposes.16-22 For example, for patients with a compressive optic neuropathy (e.g., optic nerve tumor, thyroid ophthalmopathy) or papilledema (e.g., idiopathic intracranial hypertension), serial evaluation of the RNFL might provide important information regarding progression of disease. OCT assessment of the peripapillary RNFL in our experience seems to correlate with the extent and location of the visual field loss in patients with an optic neuropathy. It is sometimes difficult to grade the degree of both optic disc edema and optic atrophy with just the ophthalmoscope. Although serial disc photographs over time are helpful, the OCT can provide quantitative evidence of stability, improvement, or worsening of RNFL thickness over time that might be difficult to judge with the ophthalmoscopic alone.18-20

Another unique application of OCT that might be helpful in neuro-ophthalmology, is the detection of bow-tie or band optic atrophy. Band atrophy is notoriously difficult to diagnose with the ophthalmoscopic or even photographically. OCT has been useful in defining the clock hours of atrophy that correspond to the RNFL loss in band atrophy. This might be useful in patients with a lesion producing a homonymous hemianopsia in whom an optic tract localization might be suspected.16-17

Correlating ophthalmoscopic appearance to structural change in the RNFL

Case Two

A 40-year-old asymptomatic female presents to her ophthalmologist and is found to have 20/20 acuity OU. There is no relative afferent pupillary defect (RAPD). Automated visual field testing is normal OU. Corneal pachymetry, gonioscopy, and diurnal measurement of the intraocular pressures were normal OU. Ophthalmoscopy shows a cup to disc ratio of 0.8 in each eye but the cup is symmetric in each eye. There was a 'hint of temporal pallor' in both optic nerves.

The ophthalmologist is often confronted with patients with an increased cup to disc ratio ('glaucoma suspect') or physiologic optic disc pallor. Normal visual acuity, visual field testing, and pupil (e.g., no RAPD in a unilateral case) exams are reassuring evidence against optic nerve pathology but measurement of a normal RNFL on OCT is additional ancillary support for physiologic variant in these cases. Photographic documentation and stability in RNFL on serial OCT measurements
over time can provide additional confirmation of the diagnosis. In our case above, the patient had a normal OCT OU and was followed clinically without change over several years.

In other patients with suspected glaucoma (e.g., ocular hypertension) there may be a concomitant anomalous optic nerve appearance that might preclude accurate assessment of glaucomatous cupping (e.g., tilted, hypoplastic, optic nerve head drusen). In these cases, there may be a visual field defect that may be due to the primary and static optic nerve pathology or might be due to acquired glaucomatous loss. Differentiating glaucomatous cupping ophthalmoscopically or photographically in these anomalous nerve heads can be difficult if not impossible. Assessment of change in RNFL over time on OCT might be helpful in such cases.23-27 Demonstration of stability in serial RNFL measurements on OCT provides reassurance that the glaucomatous component is not present or stable.

Similar to the assessment of RNFL loss in optic neuropathies, measurement of RNFL thickening can be useful in differentiating true papilledema from pseudopapilledema. Although measurement of the RNFL may be increased at baseline in both conditions, serial assessment over time might show stability (i.e., pseudopapilledema) or progressive increase in RNFL thickness (i.e., true papilledema).27

Prognostic information for patients with compressive optic neuropathy

Patients with compressive optic neuropathy might benefit from pre-operative (i.e., surgical decompression) assessment of the RNFL. Presumably, patients with better preserved RNFL have less permanent structural damage and may be more likely to improve after intervention. The prognosis for recovery after compressive optic neuropathy may depend on a number of factors (e.g., age of patient, vasculopathic risk factors, degree of decompression, duration of visual loss, presence of optic atrophy). For example, consider two patients with the same visual exam and both with a compressive optic neuropathy from an anterior visual pathway meningioma (20/80 vision OD, a relative afferent pupillary defect, a relative central scotoma, and mild optic atrophy OD in both). Patient one has a normal RNFL on OCT but patient two has a markedly reduced RNFL. The prognosis for improvement after surgical resection might be better in patient one.

Summary

OCT has many potential uses in neuro-ophthalmology including: 1. Differentiating macular from optic nerve pathology in unexplained visual loss; 2. Following change in RNFL thickness over time in different optic neuropathies; 3. Correlating optic nerve appearance (e.g., glaucoma suspects, or patients with possible optic atrophy or pseudopapilledema) with RNFL thinning or thickening; and 4. Providing additional prognostic information prior to decompression in compressive optic neuropathy.
References

Round Table

The pale nerve

Moderator: Andrew Lee, MD
Panel: Chris A. Johnson, PhD
Eve Higginbotham, MD
Harry Quigley, MD
Marc Lieberman, MD

Dr Lee: Consider a healthy 55 year old man found by the optometrist to have a visual field defect and pale optic nerves, 20/25, no afferent defect, slit lamp was normal and intraocular pressures of 18 (Fig. 1). Which of these nerves in this patient would lead you to (a) image; (b) not image; or, phrased another way, how do you judge rim pallor in the setting of optic nerve cupping?

Dr. Quigley: Disc A: this eye looks to have a large cup-disc ratio. It is a relatively large disc in diameter. We are not talking about disc diameters here today, but as soon as you look at a disc, try to categorize a disc as being small, medium or large. I would expect to have a larger physiologic cup in this one (A) than in that one (B). Disc A is a large optic disc in terms of diameter, and what that leads to is sometimes a cup-disc ratio that is in the range of 0.8 even on a physiological basis. I estimate the size of the optic disc based upon the relative diameter of the blood vessels compared to the diameter of the disc. If the disc looks like it is completely jammed full of blood vessels with no other space there, it is a small disc. If the vessels look like they are lost somewhere on the edge of the disc and there is this humongous big area in the middle, then it’s a large disc. The problem is that Disc C also looks pale to me in the remaining rim. I would have expected this part here (pointing to the temporal border) … beware, there’s a scleral halo here that’s not the disc, the disc starts where that dark line is… but there is no other real rim there. I am concerned that Disc C is more neurologic, especially because those vessels aren’t excavated. The vessels don’t fall over a rim; they are just sort of lying there a little bit.

Dr Lee: Which is more worrisome to you, pale rim, pallor more than cupping, or not very deep cupping, or are they all the same thing?

Dr Higginbotham: All three of those characteristics would be a concern. If I have more pallor than cupping, if I have a pale rim that I couldn’t account for by history that would be a concern. Disc A looks more physiologic to me. The rim tissue...
Figs 1a-c. These images of discs are representative photographs of optic disc cupping with pallor and are for illustrative purposes only.

appears to be somewhat even. Of course, it’s always hard to tell without having stereo disc photography. The second one, Disc B, appears more excavated than Disc A. Disc C, I don’t know, I need more information on that third one.

Dr Marc Lieberman: In Disc A, there is a nice quality here that is characteristic of normal optic nerves, namely, the horizontal cup is larger than the vertical dimension of the cup. That’s characteristic of a normal nerve, and especially with a large disc. That looks very much like a normal configuration. The other thing that hits me is in Disc B, that inferior vessel that is leaving the major vein and going out and exiting, it looks like it is going out and draping down over a rim and I think that rim probably goes all the way out to the edge. Disc B, with the inferior temporal rim loss, looks glaucomatous to me. Disc C looks pale, whatever rim is left.

* These are not the original slides from the symposium due to data corruption and Dr. Lee apologizes for the substitution. Dr. Lee believes that they demonstrate the teaching points, however.
Dr Lee: I didn’t mean to confuse you with diagnostic uncertainty in the photographs, but to show you that it is difficult. The thing we read in the books, which is easy for me to write, rim pallor equals non-glaucomatous, is actually a hard thing to discern in the real world.

Dr Lieberman: This is why you should never have glaucoma and neuro-ophthalmology guys at the same meeting.

Dr Lee: When do you image normal tension glaucoma? Rim pallor?

Dr Higginbotham: Among some of us.

Dr Lee: Rim pallor, everybody is in agreement with that? If the rim is pale you’re going to image that?

Dr Quigley: Were you going to do a field on the patient or you couldn’t afford that?

Dr Lee: So you are saying you have to have all these criteria linked together to make the decision to image?

Dr Quigley: No, but if you want me to tell you when I want to image somebody, I would like to have at least the disc and the field finding. If the patient couldn’t do a field test, sure, then you have another hand behind your back. But that happens maybe two percent of the time. The other 98%, you can get some kind of an idea of the visual field.

Dr Lee: Is there any rim pallor that you would accept and not image?

Dr Quigley: Yes, there are some very advanced glaucoma discs in the 0.85 or greater range where now there is almost no rim left ... that advanced disc, it could start looking pale in a glaucoma circumstance.

Dr Lee: I would agree with that. Eve, if someone is 0.95 or more, can you really say anything about their rim?

Dr Higginbotham: No, not necessarily. He won’t have a lot of rim there to actually say very much about. I need to know more about each of these issues as it relates to the visual field and the history.

Dr Lieberman: Bob Schaefer used to teach that if you have unilateral low tension glaucoma, it’s a meningioma unless proven otherwise. The one thing that is really crucial to me is whether the optic neuropathy is unilateral. If it’s a bilateral condition I don’t think imaging is going to provide a high positive yield.

Dr Quigley: I don’t want to disagree with Bob Schaefer, and he is my hero, but most persons with glaucoma at normal pressure present unilaterally. Many, many more present unilaterally than bilaterally. If you look numerically at the number of meningiomas compared to those who have asymmetric normal tension glau-
coma, it is like one meningioma for 10,000 persons with normal tension glaucoma. That means that you are going to disprove in 9,999 people that they don’t have the meningioma.

Dr Lieberman: I’m sorry Harry, I guess I didn’t get all that. I am not trying to say that they are always going to be symmetric in their cupping, but in low tension glaucomas, usually you will see in the fellow eye something that is abnormal, even if it’s lesser cupping.

Dr Quigley: It’s very disturbing when you see heavily asymmetric glaucoma. You think – how can it be so asymmetric? I can think of about four patients with their names off the top of my head who are people I have watched for ten years now with really bad typical glaucoma in one eye at normal pressure, and they have responded to being stable with pressure lowering and the other eye has a normal disc and field. I believe they have risk factors in one eye that they don’t have in the other eye. They have lousier connective tissue on one side than the other. Do any of you have a knee that hurts? Is it both knees? Not necessarily. You can have lousy connective tissue in one knee and not the other one.

Dr Higginbotham: Andy, if I might comment, of the six items on your list (rim pallor; strictly unilateral; acute vision loss; hemianopic field; mismatch of field and optic cup; visual acuity loss), I would highlight rim pallor and temporal course. If I have a patient demonstrating a rapid significant decline in their visual status, then certainly I would want to go ahead and image that patient.

Dr Lee: My point with the rim pallor was, I don’t think I personally can judge remaining rim pallor once the cup to disc ratio is 0.95 or more. Field type, severity, location I think is what you were alluding to in terms of integration of the clinical data with what you see. If the cup is 0.4 and the field is blacked out that’s not going to match. I use hemianopia and central scotoma. I would be interested to hear what the rest of the panel says on location type field defect.

Dr Quigley: You mean if it respects the vertical midline? If it respects the vertical midline you have to do a neurologic work-up. Patients can hysterically or in a purposeful way actually produce a neurologic looking field defect on the Humphrey machine. I have a fellow who figured out how to do it and I have several patients who consciously or unconsciously do. One lady produced a bitemporal field defect for us, hysteric, and then forgot what she had done and gave us a homonymous field defect the next time. She was the index case for figuring out that you can do it.

Dr Lee: I would just add that the machine actually prompts you and helps you make hemianopic field loss in the standard perimetry of Humphrey.

Dr Quigley: I would have you image some other people who have pallor out of proportion to cupping or they have a field defect that is not typically glaucomatous, and their eye pressure is 32. You should be imaging people who look like they have neurologic disease, regardless of what their eye pressure is.
Dr Lee: I think Harry made an important point about IOP. If it’s a neurologic field and they have high pressure, it doesn’t matter, it’s still a neurologic field. The reverse is also true, if it’s glaucoma and low pressure, that isn’t neurologic disease.

Dr Higginbotham: The patient that I presented, the second patient, is the fastest patient I have had to progress in twenty years. This patient essentially went downhill in three years, after not having had much of a change. That’s why you have to do several visual fields, so you can get a sense of what the tempo of change may be in any individual patient.

Certainly you can have asymmetric disease, so I would have to say that that’s not a big issue for me. Invariably, especially in Baltimore, you could have a lot of angle recession glaucoma that can present as significant disease in one eye versus the other.

Dr Lee: If it looks like glaucoma, I don’t use ‘asymmetric neuropathy’ to image. Acuity loss?

Dr Quigley: I think it is very important. The case I presented in one of the talks I gave today demonstrated that visual acuity was the key. The cue was that the patient had very modest visual field defect, but had 20/60 visual acuity. There is something wrong there. Glaucoma patients are typically 20/25, 20/30, even with advanced field loss, on average.

Dr Johnson: It is very important to realize that nerve fiber bundle type defects, glaucoma looking type visual field defects, can be associated with other types of optic neuropathies. You showed a very obvious case of optic nerve head drusen earlier, and that isn’t going to be missed. But you can have very subtle drusen and you can have someone with elevated pressure with optic nerve head drusen and visual field defects that look like glaucoma, and that is true for other optic neuropathies as well. It is important to try and put the disc and the field together for an accurate assessment and diagnosis.

Dr Higginbotham: If I could comment on the acuity loss, and we haven’t really talked about multifocal ERG, but I have used that technique as a way to really try to understand what is happening to the vision centrally.

Dr Johnson: I think that multifocal ERG is helpful for retinal disease and looking at retinal anomalies. Multifocal VEP seems more useful for glaucoma. For glaucoma per se, we haven’t found Multifocal ERG to be that useful, and we have tried very hard with that.

Dr Lieberman: Twenty years ago in Vancouver there was an interesting study that looked at different patterns of the velocity of visual field loss, and these were Goldmann visual fields, and it was pretty much on the analogy of multiple sclerosis, that sometimes MS will just go down an icy slope rapidly and other times will be episodic, and sometimes is a staircase that is fairly predictable. Eve’s sec-
ond case raises the question whether these episodic visual fields are really just episodic noncompliance episodes. Chris or Harry, are there any updates about the different flavors of visual field loss over time?

Dr Johnson: We have tried using a lot of different mathematical models, multivariant models, nonlinear models and other things to characterize loss, episodic logarithmic loss, exponential loss, and linear and so on. I have combined data sets to increase the sample size by sevenfold, so that we had a much larger sample to choose from, we haven’t found anything that does better than linear loss and that’s what I feel right now gives the best estimate of visual field loss. There is nothing I have seen in the literature that can surpass a linear progression of loss for glaucoma.

Dr Quigley: There are some clinical pearls here. The first is I’m not sure that a practitioner taking care of patients cares very much whether visual field progression proceeds with little stair steps or gradually or sigmoid, or whatever. I don’t think from the clinical perspective it matters very much to someone who is monitoring the visual field once a year, because it is going to look like it is changing based on how many samples of the phenomenon that you’re looking at. If you have five fields, you will never know if it is a stair step or if it’s a sudden… it is rare though for glaucoma patients suddenly to get worse. I mean suddenly from one day to the next, even from one month to the next. Over the course of a year, absolutely. Pseudo-exfoliative glaucoma patients can get rapidly worse. The kind of patient Eve presented with pressures of 36 off meds can get worse relatively rapidly, especially when they are already damaged.

Dr Johnson: The critical factor from a clinical perspective is has the visual field changed, and you need to confirm and do a lot of visual fields. But how has it changed? Has it changed linearly or nonlinearly? That’s really not a critical issue from a clinical standpoint. It is whether it has changed or not.

Dr Higginbotham: I think we have to recognize the issue of compliance as well, as I alluded to in my last case. There is something that I call white coat controlled glaucoma. There are patients that will only take their meds just before they come in to see you. It’s hard to really put your finger on those patients. As my one patient indicated, he really fooled me for a long period of time, because I am sure there were periods where he didn’t take his medicines, and that’s why he had such progressive disease.

Dr Lee: My approach from the neuro-op side to this question is, if it quacks like a duck and it walks like duck and swims like duck, it’s a duck. If you have a cup and visual field that looks like glaucoma, I don’t care what the pressure is, I am not going to image that person, I am going to send him back. I can tell you, a neuro-ophthalmologist is a heck of a lot cheaper than an MRI scan.
Questions and Answers

Presiding Physician: Jill Koury, MD

Dr Koury: Fifteen years ago the Vancouver glaucoma team described different patterns of long term visual field loss, episodic, general decay, staggered stepwise loss, any merit to an update being done on this report?

Dr Higginbotham: Yes, that was actually Marc’s question. It’s hard to really know, but it seems most patients are linear, but you can get some variability there.

Dr Koury: Are there any medications you would use, or any medications you would stay away from in patients with low tension glaucoma?

Dr Higginbotham: That’s where I really have to talk with the PCP. Many of these patients have systemic hypertension. We have to make sure that they are not using meds that will drop their blood pressure, such as a systemic beta blocker. I don’t use calcium channel blockers because the data is just not there and they are not easy drugs to use. There are a lot of potential side effects.

Dr Lee: Would you say the same thing about Timoptic?

Dr Higginbotham: I use beta blockers. That’s one of the reasons why I chose not to be part of the Collaborative Normal Tension Glaucoma Study, because I had concerns about not being able to use a topical beta blocker in that trial.

Dr Lieberman: I think one of the major implications of Dr Quigley’s presentation that low tension glaucoma is just part of the primary open angle glaucoma spectrum is that I personally don’t see any reason to exclude any glaucoma medication for patients with low pressures. I think the burden of proof is on Dr Drance and Dr Anderson to prove that timolol is contraindicated in those particular patients. I don’t think there is any evidence for it. If you have a patient with low tension glaucoma and you are used to using a beta blocker, I don’t see any reason why you shouldn’t.

Dr Quigley: Yes, in 1984 when the study was designed, we thought there was a possibility that beta blockers decreased retinal and optic nerve blood flow. We now know almost conclusively that they improve retinal and optic nerve blood flow. Timolol clearly improves retinal blood flow. The second fallacy was that persons with glaucoma at normal pressure had something wrong with their vasculature. I just made the argument for you that there is something wrong with their connective tissue, at least, and they may have something wrong with their vasculature. The
normal tension glaucoma study could not find anything but migraine that was associated with those who progressed. The large set of risk factor studies I presented earlier do not indicate that major cardiovascular disease and lots of other stuff related to it are in fact related to glaucoma at normal or high pressures.

Dr Lee: Do you even ask about Raynaud’s, migraine?

Dr Higginbotham: In my review of systems I do.

Dr Lee: And what do you do with the information?

Dr Higginbotham: I write it down.

Dr Lieberman: Whenever you go back and look at the criteria, for example in the OHTS study for a history of migraine, they are never using the criteria that the neurologists use, which are rather specific. The ophthalmologists ask “Do you have migraine headaches?” and when people say yes, I have a migraine – to me there is tremendous lack of specificity in that particular question of the history.

Dr Higginbotham: I consider it as part of the thorough historical background of that patient. If a patient demonstrates rapid progression of their disease, then migraine or Raynaud’s may be an important component of their disease.

Dr Koury: Dr Quigley says that low tension glaucoma does not exist. Dr Higginbotham says ethnicity has little to do with glaucoma. Then how do you explain the very high rate of glaucoma with low pressures among people of Japanese ancestry?

Dr Quigley: It’s a very interesting thing. It’s a tonometric artifact. There is considerable information now on the fact that Asian persons by tonometry read lower on average by about a 1.5 - 2 mmHg than do persons who are European or African derived. Paul Foster has written a paper out of his studies in Singapore with cannulation of the eye in the operating room and measuring tonometric eye pressure. There is a systematic under-read on the eye pressure in this Asian population. Almost surely what is going on is that their real eye pressure is 15.5, but is measuring 13.5. Interestingly, this finding is not due to a difference in the cornea thickness distribution in Asian persons compared to European persons. The corneal thickness does not provide you the answer. It’s a difference in corneal bioelasticity.

Of course, if a Japanese group says that the top of the normal pressure curve should be 21, using the European value, and then they apply that to the pressure distribution of Japanese people, instead of 50% having so-called low tension glaucoma, they would have 80% with so-called low tension glaucoma, because it is reading off the wrong scale and using the European cut-off. I have spoken with Yoshiaki Kitazawa, who is one of the godfathers of glaucoma in Japan. I asked, “Yoshi, why don’t you use the so-called 2 standard deviation cut-off for Japanese people, which would be 18?” He said, “Well, I wouldn’t think that any of the major journals, the Archives of Ophthalmology would accept our doing that, because they would think that we were using the wrong scale, because the Europeans dominate everything.”
Dr Higginbotham: It is important to individualize treatment and certainly once you start talking about populations, it is really hard to define what should be the population. Specifically, measure the characteristics of the individual patient and take it from there. Look at the optic nerve, look at the visual field, measure the corneal thickness, and that’s what you need to follow.

Dr Koury: For the treatment of optic neuritis – any reason why oral steroids would be worse than placebo while IV steroids are better?

Dr Lee: Two issues: one is the steroid doses were not equal. The oral prednisone dose in the study was 60 mg to 80 mg of prednisone, which is not the same as 1000 mg of intravenous methylprednisolone. The second issue concerns the route of drug administration. The intravenous route is going to avoid any first pass effects that occur through metabolism in the liver.

Dr Koury: Is there a dosage of oral steroids that will do the same as IV?

Dr Lee: That question has been looked at and the Japanese and European optic neuritis treatment trials used oral steroids at a dose of 500 mg of methylprednisolone, and that dosage did not increase the recurrence rate of optic neuritis. Different drug though. Methylprednisolone, prednisone, not the same thing, different dose, but you could theoretically use oral methylprednisolone at a higher dosage in place of intravenous.

Dr Kellum: I can understand why IV steroids work better than oral steroids; it may be related to the dose, but why would oral steroids, if you put them in a hierarchy, oral steroids, placebo, IV steroids, why would oral steroids have a negative impact?

Dr Lee: I quote Neil Miller on this and Neil says you go out hunting and you are hunting for bear. You shoot the bear, but you don’t kill him; you just wound him with the oral steroids. Which is worse, that you didn’t shoot the bear at all, or that you shot and you missed or you wounded him. A wounded bear comes back angrier and worse. So presumably the oral steroid, whether it is dose effect or route administration, is not sufficient to kill it. It comes back angrier than if you hadn’t gone hunting at all.

Dr Koury: What are normal and abnormal values for ESR and CRP?

Dr Lee: The question concerns values of an abnormal sed rate and abnormal CRP, if you look in your lab it will say ESR 0 to 20 mm/hr. We know that the sed rate is susceptible to all sorts of artifacts induced by the hematocrit. After all, you’re just measuring the rate of sedimentation of red cells. If you have less red cells you’re anemic – that’s going to change the sed rate. In addition, when you get older, your sed rate goes up normally. There are age adjustments that can be done on the sed rate to make up for that and one standard adjustment is age plus ten divided by two, if you are a woman, age over two if you are a man. This doesn’t account for all the other things, like your hematocrit and all the proteins that are floating around your body or whether you have diabetes or renal failure. There is no absolute real number I can give you. But if you say okay, I just want to have a number no matter
what you say, 33 for the sed rate. The CRP is laboratory dependent and it is made worse by the fact that we have high sensitivity CRP, which is a totally different test. That’s for cardiovascular risk factors. In our laboratory, a CRP of less than 0.5 is the normal, but in some laboratories the decimal place is shifted and five is the number. Look at your own individual laboratory.

The real answer to your question concerns the sensitivity and the specificity of the test can change if you set the bar higher or lower. Suppose you set the ‘normal’ sed rate at 100, and you are going to use that cutoff to detect giant cell arteritis. You will detect fewer cases of giant cell arteritis, your sensitivity will be low and the specificity will be high. If you set the sed rate cutoff to 22, then your sensitivity goes up, finding more giant cell arteritis, but the specificity drops.

Dr Koury: Dr Lee, are you saying that we should get a stat sed rate and a C-reactive protein on all patients with anterior ischemic optic neuropathy, or just patients when we have a clinical suspicion for giant cell arteritis, since you can get a false positive elevated ESR, for example in patients with renal failure?

Dr Lee: So this is back to the question, what is the most powerful predictor of the disease actually being present? Pretest likelihood of disease, regardless of the test that you perform. If the pretest likelihood of disease is two percent, the person is 35 years old, has diabetes, hypertension, then don’t order the test, because the chance of that person having giant cell arteritis is low. Even if the test is positive, in this case a sedimentation rate, that doesn’t move the post-test likelihood of disease beyond a threshold that you would consider treatable. Conversely, if you have a 90-year old person with headache and scalp tenderness, jaw claudication, bilateral disc edema and the sed rate comes back too, the pretest likelihood of disease is 95%, and a normal sed rate in that setting only moves the post-test likelihood of disease to like 90%. You are not going to use the lab to kind of make this up or down kind of thing. If you think the person absolutely does not have giant cell arteritis, then you probably could get away with not ordering the sed rate and CRP, but the fact of the matter is, most people are in between. You have the 52-year old person with nonarteritic AION. You order the test to try and move the post-test likelihood of disease towards one of the diagnostic spectrum. In reality, the pretest likelihood of disease is much more powerful than any lab test.

Dr Koury: With retro-bulbar optic neuritis, is it important to start IV steroids within one week, is any time frame vital for success?

Dr Lee: Intravenous steroid speeds the rate of recovery, but you are talking about speeding the rate of recovery of weeks. If you are already three weeks in, you are not really gaining a lot from intravenous steroids if you are using the treatment to speed rate of recovery. If, however, you believe that intravenous steroids reduce the rate of clinically definite MS, which was shown in the optic neuritis treatment trial at year two, but that effect wore off by year five; or, if you are going to consider the patient for interferon therapy, that is, they have an abnormal MRI scan, then it is probably okay within a two week window or maybe even a little bit more. It just depends on what you are using the intravenous steroid therapy for.
**Questions and Answers**

**Dr Koury:** If an retro-bulbar optic neuritis patient had other episodes, numbness or other symptoms, are IV steroids indicated?

**Dr Lee:** In the optic neuritis treatment trial and in the CHAMPS study, the monosymptomatic event, those subjective complaints don’t count as an event. Clinically definite multiple sclerosis means you had two documented objective neurologic attacks. Just saying I had numbness for a week when I was in college doesn’t cut it. You should not be using that as a driver for intravenous steroid therapy. What you should be using is their MRI scan. The MRI scan is a much more powerful predictor of multiple sclerosis than whether I had subjective numbness in my right hand in 1972.

**Dr Koury:** Would you use IV steroids for two or more episodes of retrobulbar neuritis within the first two to three years?

**Dr Lee:** These are questions that are not answered by the clinical trial. If you have recurrent optic neuritis, that debate is did you have one lesion or two. Multiple sclerosis – multiple lesions separated in space and time, that is, they have to be at different times and they have to be different spaces. If the attack is in the same space, technically that doesn’t count as clinically definite multiple sclerosis. Would you use that as a driver for intravenous steroid therapy? Maybe.

**Dr Koury:** Someone asked about the reliability of using Tono-Pens in monitoring open angle glaucoma.

**Dr Higginbotham:** Tono-Pens can be very unreliable and certainly I think we all have experienced that. I have found there to be significant variability. Tono-Pens tend to underestimate the pressure at higher levels and overestimate the pressures at lower levels, that is less than six. You need to have other methods at least available, not including the Schiotz.

**Dr Quigley:** An experienced observer with a Goldmann applanation tonometer, an experienced observer using a Tono-Pen will find that their variability in the measurement is much lower with Goldmann applanation tonometry. I urge you to use Goldmann applanation tonometry in every situation in which you can. In situations when you have an unusual cornea, a somewhat uncooperative or young person, Tono-Pen becomes very useful.

**Dr Lieberman:** Dr Palmberg swears by the Tono-Pen and I personally find it is useful for generating lottery numbers, because it is fairly random in my hands. I know that there was a study comparing different tonometers using the same kind of cannulation technique in phaco patients. The pneumotonometer seemed to have the best correlation of actual manometric pressure measurements. The pneumotonometer, which no longer runs on gas canisters but sets you back five grand, is a very sweet way to get accurate pressures with bad corneas and may or may not be independent of this central corneal thickness.
Glaucoma
Risk factors for open-angle glaucoma

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Risk factors are attributes of a person at risk or of their environment that make disease more likely to occur. Some risk factors are immutable (such as chromosomal gender), while others are variable, and even amenable to change through therapy or behavior modification. The understanding of risk factors provides clues to causation, but the complexity of most disorders typically frustrates direct, simple cause and effect linkage. The causes of disease in each individual who share a common phenotype may be different or may share some risk factors but not others. The sequence of events that cause a disease is not simple and linear, though some factors are present prior to others, and the entry of the last risk factor into the picture is followed by a period before disease appears known as the induction period. So, the cause of open-angle glaucoma (OAG) is not simply ‘mechanical’ or ‘vascular’, but deserves a more sophisticated analysis. Risk factors for open-angle glaucoma will be considered here in a brief format, as a more definitive report on this subject is presently in preparation for publication.

Age is a consistent risk factor for OAG, the older the person, the more likely the disease. Prevalence of OAG rises more than linearly with age. This may be a combination of a number of features related to age. The relevant body tissues age, and older retinal ganglion cells (RGC) may die faster than younger ones. Age expresses the length of time that the person is exposed to other risk factors, increasing the chance that they will lead to disease. The longer the sufficient component risk factors are present for a person, the more likely that disease will be present. Age modifies the strength of association of other risk factors, for example, hypertension.

Gender shows only modest association with aspects of OAG. Some studies show that men are somewhat more likely to develop OAG or to undergo progression, while others suggest that women are at greater risk for worsening. We must keep in mind that men and women differ only in 60 or so genes on the Y-chromosome, and that the gender-related differences in OAG may relate as much to culturally determined behaviors that are gender-specific as they do to hormonal...
influences that are biochemical. Men may be less likely to seek preventive care, or
doctors may behave differently toward female patients.

Ethnicity plays an important role in the literature of OAG, but many experts
now question whether we can actually distinguish humans on the basis of an
artificial construct called race. With particular reference to black or African-de-
derived persons, there is cultural and historical baggage associated with designating
persons differently. We speak of these categories as if they are genetic, yet there
are no consistent DNA markers that distinguish us, and some of the risk associ-
ated with physical appearance may be socio-economic or cultural in origin.1

Having expressed those reservations, we have found that African-derived per-
sons in East Baltimore, Maryland, and African villagers in Tanzania, East Africa
share a prevalence of OAG that is four times higher than that of European-de-
derived persons.2 Across an ocean of differences in diet, education, environment
and attitudes, this similarity speaks to a genetic component to this shared risk.
East Indian, Chinese, and Europeans seem to have similar OAG prevalence. The
differences for African-derived persons may relate to having larger diameter optic
discs with smaller numbers of RGC, thinner corneas, poorer response to topical
drugs, or poorer access to care.

Those who have family members affected by OAG are ten times more likely to
develop the disease.3 To say that this is a genetic effect is appropriate, though one
must leave open the possibility that families share more than genes, and the
environmental impact on a common genetic endowment may magnify the associ-
ation within family units. The linkage is significant for siblings and parents, but
more distant relationships are not so well studied. The likelihood that a patient
who gives a ‘positive’ family history is actually correct that the family member
has OAG is far from reliable. But, family members are known to share similar disc
parameters, IOP levels, and refractive errors. And, we now know that at least two
genes, optineurin and myocilin,4 when mutated in particular ways, are associated
with a small number of cases of OAG.

The IOP, both its level and its fluctuation range are consistent risk factors for
OAG, though it is incorrect to equate this with ‘elevated’ IOP, as was commonly
done in the past. POAG can occur at all levels of IOP. The higher the IOP, the
more likely POAG is to occur, the more severe it is, and the more likely it is to
progressively worsen, even when IOP is consistently in the range considered normal.5
The association between IOP level and risk of development of POAG is a shal-
lowly increasing exponential relation, with no ‘break-point’. The transition from
the normal IOP in a population to the level considered elevated does not distin-
guish those below and above this zone from each other. The past use of the terms
normal tension glaucoma is an anachronism. It is now recognized that a substan-
tial minority of POAG occurs at normal levels of IOP and the definition of POAG
now does not include an IOP criterion. A causative linkage between IOP and
POAG has been firmly established by the additional facts that lowering of IOP
decreases onset or progression, and by the production by increasing IOP in ani-
mal models of a disease identical to human glaucoma.

Other ocular anatomic features are risk factors for OAG. These include exfo-
ilation syndrome and pigment dispersion syndrome. Myopia, even at relatively lower
refractive errors also confers increased risk. The thinner cornea has recently been
recognized as an important factor, at least because it causes artificially lower IOP
Risk factors for open-angle glaucoma

measurements by applanation tonometry, but also perhaps as an indication of poorer responsiveness to the stresses on the eyewall that associate with OAG. The larger the optic disc diameter, the more likely OAG is to occur, probably as a biomechanical disadvantage of a larger weak spot in the posterior globe where axons exit. It seems that peripapillary crescents of non-junction between disc margin and Bruch’s membrane may also increase risk, though they are very common in the general population.

There has been considerable study of whether personal behaviors affect OAG risk. Interestingly, nearly all of them seem unrelated. This includes no association with caffeine, alcohol, or cigarette consumption, and no consistent relationship with body mass index. The failure to have an association with cigarettes, which are highly related to two other major eye diseases, cataract and macular degeneration, is interesting. We frequently do not pay attention to ‘negative’ risk factors. But here, one must wonder why the definitive effect of smoking (presumed to act through generation of excess free radicals) has no effect on OAG. Does this suggest that free radicals are rarely of import in OAG pathogenesis? Some things may matter, for example, exercise lowers IOP, so couch potatoes should be urged to start a program. But, it should not include hanging upside down or any other behavior that raises episcleral venous pressure – such as playing a wind musical instrument. The latter raise IOP and may be associated with OAG.

Some non-glaucoma medications are OAG risk factors. On the good side, therapies that lower cholesterol were recently linked to lower OAG risk. It is well-known that oral and topical corticosteroids raise IOP. The steroid nasal sprays and inhaled steroid products must also be treated as risk factors as well.

Other clinical diseases and states are also risk factors for OAG, though none of the relationships are strong or simple. Thyroid disease, migraine, and sleep apnea are all reported associations, as are both late menarche and early menopause in women. The story with hypertension used to be simple, it was a risk factor. Most studies now agree that it is not a global risk factor, but only when considered together with age and IOP. Younger persons with hypertension are less likely to have POAG, while older hypertensives were at greater risk. This suggests that the duration of hypertension is an important modifier of the effect of blood pressure on POAG. Furthermore, low blood pressure is also highly associated with presence of POAG when it is near enough to the level of IOP that their difference (blood pressure minus IOP = perfusion pressure) falls below a certain level (below 50 mmHg and particularly below 30 mmHg).

Diabetes was also formerly considered an OAG risk factor, but most studies now show that it is not. Furthermore, there is the intriguing fact that diabetics have higher mean IOP than non-diabetics. Hence, they should have more OAG, unless there’s some protective aspect of diabetes for OAG. This sounded far-fetched until the Ocular Hypertension Treatment Study found that diabetes (non-retinopathy, early disease) was protective for development of initial damage. One speculation is that early diabetes causes leakage of serum proteins into the retina that are actually neuroprotective.

Now that we have listed factors that are linked to OAG in some way, we should be more sophisticated and realize that some things would make initial OAG more likely, some would make progression more likely, and some would relate to response to therapy. The list might not be the same for each. In fact, some
might be detrimental for incidence but be beneficial factors in response to treat-
ment (e.g., pigment dispersion). We will need to dissect the roles of risk factors in
greater detail.

The future holds the use of risk factors in calculations that predict the most
likely future course of patients as they enter the care system. We will use the
available information on the patient and risk associations for them based on past
data to generate the level of concern for treatment, i.e., the target pressure and
whether we wish to add neuroprotective treatments that are developed indepen-
dent of IOP-lowering. This risk assessment will be continuously updated as ex-
amination information is accumulated on the patient to maximize the chance that
we do the least harm.

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Does either sex or ethnicity matter in glaucoma?

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Introduction

One may consider the question regarding the potential influence of either sex or ethnicity on glaucoma one that is purely academic. Undoubtedly, the influence of intraocular pressure on the course of glaucoma is unquestionable. Several well-done clinical trials now exist which establish intraocular pressure as a major determinant of the glaucomatous disease process. The Ocular Hypertension Treatment Study\(^1\) has documented the protective benefits of treating patients with an elevated intraocular pressure but ‘normal’ optic nerves and ‘normal’ visual fields. The Early Manifest Glaucoma Treatment Study\(^2\) confirmed the benefit of treating patients with glaucoma. Therefore, is there a need to look any further for significant contributory factors for either the differences in prevalence or treatment of glaucoma?

Considering that there are differences in the prevalence of glaucoma, age of onset, rates of progression and response to treatment options, this paper will explore the potential influence that either sex or ethnicity may have on the glaucomatous disease process. The issue of sex may be a little easier to tackle than the issue of ethnicity. There are biological differences between the sexes; on the other hand, the differences that separate the various ethnic groups are significantly related to nonbiological factors. Considering there is no consensus in the literature with regards to either question, both questions are difficult to answer.

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Does sex matter in glaucoma?

Before exploring the potential influence that sex may have on glaucoma, it is helpful to clarify the rationale for using the term, ‘sex’ rather than ‘gender.’ ‘Sex’ is a biological classification that is based on reproductive organs and functions that are derived from the chromosomal composition of an individual. On the other hand, ‘gender’ refers to an individual’s representation as either male or female, which may be shaped by environmental or social influences. Thus, since this report is more focused on the true biological influences rather than the environmental influences on the eye, this discussion will use the term ‘sex’ rather than ‘gender.’

When considering the influence of sex on the glaucomatous process, there are very few sources which one can refer to. Recently, the Institute of Medicine published a report regarding the potential influence that sex may have on the nonreproductive areas of biology. This monograph, entitled ‘Exploring the Biological Contributions to Human Health: Does Sex Matter?’, reviews a number of disease states that are influenced by the sex of the patient. Certain diseases, such as lupus erythematosus, sarcoidosis, and migraine headaches with auras, are known to be more common in women than in men. Women respond differently to painful stimuli depending upon the timing of the insult during their menstrual cycle. Women have more ‘silent’ myocardial infarctions than men, and unfortunately are twice as likely to succumb to a cardiac event if it occurs prior to the age of 65. Furthermore, research indicates that women may even recover their language abilities more quickly following a stroke than men. Despite being ‘advertised’ as a comprehensive review that spanned most organ systems of the body, there was no mention of the potential influence of sex on the eye.

What have we learned from population studies, sex, and glaucoma?

Population studies fail to provide a clear consensus regarding any sexual predilection for glaucoma. In the studies conducted in Framingham, Barbados, and in the Rotterdam Study, males were noted to have a higher prevalence of glaucoma. However, females were dominant in the St. Lucia and the Blue Mountains studies conducted in Australia. There were no sexual differences reported in the Baltimore Eye Survey, the Beaver Dam Study, the Los Angeles Latino Eye Study, and the Melbourne Study. These studies, however, focused primarily on open angle glaucoma. When one considers angle closure glaucoma, there may be a greater likelihood that women may present with signs of angle closure more often than men. Foster noted in a population screened in China, that female ‘gender’ proved to be a risk factor for glaucoma, along with older age. Thus, depending upon the demographic mix of individuals studied, the data certainly will be affected.

Given the facts that the life expectancy at birth for females compared to males is longer and that glaucoma is a disease largely related to the aging process, the representation of women versus men across these studies may have influenced the findings. Moreover, socio-economic factors, the difference in the value of the health of men versus women in various populations, limitations in access to care, or poor quality of care can also influence these findings.
Does either sex or ethnicity matter in glaucoma?

Early menopause, estrogen, and therapeutic options

Related to this question of sex and glaucoma, there are three interesting points that are important to highlight. First of all, at least one study suggests that the early onset of menopause may influence the onset of disease. In the Rotterdam Study, which was conducted in the Netherlands, it was noted that women who were menopausal before the age of 45 (odds ratio = 2.6) were more likely to develop glaucoma than those who were menopausal later. The authors theorized that the loss of female sex hormones may have hastened the onset of the glaucomatous disease process. When one considers the vasodilating effects of estrogen, it is compelling to consider this theory. In fact, Harris-Yitzhak and coworkers noted a reduction in vascular resistance in the ocular vasculature of postmenopausal women who received exogenous estrogen therapy.

Secondly, women may be prone to evidence glaucomatous progression at low intraocular pressures. Indeed, in the Collaborative Normal Tension Glaucoma Study, female sex, disc hemorrhages, and migraine headaches were significant risk factors for progression of disease.

Finally, therapeutic choices may be influenced by the sex of the patient. Since postmenopausal women have a higher likelihood of developing keratoconjunctivitis sicca, the choice of therapy should be considered. For example, one may wish to avoid using beta blockers as a first choice of therapy, since this class of medication may worsen the symptoms of ocular dryness. Moreover, since carteolol hydrochloride, a beta blocker with intrinsic sympathomimetic activity (ISA), has less effect on systemic lipids than a non-cardioselective beta blocker without ISA, one may wish to choose this beta blocker in a post menopausal woman who may be at a higher risk for coronary heart disease.

Although some population studies fail to demonstrate a sexual predilection for glaucoma, there are potential influences of female sex hormones on the onset of disease and the course of one’s disease process. Certainly choice of therapy must be individualized; however, this finding provides less compelling support for considering sex as an important factor.

Does ethnicity matter?

The influence of ethnicity is more difficult to decipher, since there is no valid method of separating groups of individuals like there is for the two sexual groups. Some readers may wonder why the term ‘race’ was not used, since that is the term most often used when delineating groups of individuals. The basis for the modern day characterization of the races dates back to a Swedish physician named Carolus Linnaeus (1701-1778), who developed a system for organizing both plants and animals. He described four species of man and differences which were arbitrary and ill founded. Blumenbach, who is considered to be the father of physical anthropology, described five categories of mankind and suggested that differences were largely related to the environment. These classifications did not exist until individuals started leaving their home continents, discovering other populations, colonizing some populations, and enslaving others. To a large extent the arbitrary categorization of the human family changed the course of history.
If one fast forwards to the twentieth century, genetic data reaffirm the common roots of the human race. The fact that the world population shares 99.9% of the gene pool indicates the youth of the species and the relative lack of heterogeneity that exists.20 Given the genetic admixture that has taken place over the last 200,000 years, it is clear that the arbitrarily designed categories were far from correct. Certainly there are socioeconomic factors that are ‘race’ based, but there is no evidence there is a biological basis for these large categories.21 Thus, although far from perfect in its own right, ‘ethnicity’ may be a better surrogate to describe large groups of individuals. Although a term that is largely based on culture, it is related ultimately to the family unit, which of course is the critical source of genetic mishaps that may cause disease. Thus, for the purpose of this review, the term ‘ethnicity’ will be used rather than ‘race.’

Population studies across ethnic groups: what have we learned?

Differences in prevalence have been noted across various ethnic populations. The Baltimore Eye Survey examined 5308 individuals who were either self-reported African American or Caucasian. This study reported an age-adjusted prevalence of 4.74% for African Americans and 1.29% for whites.9 There have been several Caribbean studies that reflect a significant variation of prevalence rates from a low of 1.4% among Jamaicans,22 aged 35 years of age and older to a high of 8.8% in St. Lucia (age greater than 30)7 and 6.6% in Barbados (ages 40 to 84).5 Recently, the Los Angeles Latino Eye Study reported its results among a predominant Mexican-American population, over 40 years of age and living in La Puente, California. The overall prevalence of primary-open angle glaucoma in this population was 4.74%, ocular hypertension, 3.56%.11 However, these investigators reported an important finding. Greater than 75% of those who were diagnosed with glaucoma, had no history of the disease or had never received treatment. This finding raises the issue of whether or not socio-economic factors, or factors other than those that are considered biological, may be significant contributors to the differences in the prevalence of glaucoma across populations.

Do socio-economic factors matter?

When considering socio-economic factors, the issues are myriad. Health care coverage is a significant issue that needs to be addressed. The number of uninsured in the United States is greater than the populations of Texas, Florida, and Connecticut, combined. It has been estimated that the number of uninsured comprises 17% of the population over the age of 65 years of age. There are differences in coverage across populations. Self-reported African-Americans are twice as likely to be uninsured and Hispanics are three times as likely to be uninsured, compared to others. Factors such as education, income, and economic sector form the basis of much of the disparity in insurance coverage.23 These factors have also been correlated with patterns of health practices. Individuals in lower economic strata are less likely to reduce high-risk behavior, such as poor dietary habits, smoking, and alcohol abuse and adopt new health-enhancing practices.24 Figure 1 illustrates
Does either sex or ethnicity matter in glaucoma?

Fig. 1. This figure illustrates how specific biological risk factors can be amplified when patients must confront several nonbiological factors such as socioeconomic status and health illiteracy.

Although health care coverage is fundamental to some of the differences across populations, there are still differences that exist within the insured populations. One of the best examples of this phenomenon comes from the general medical literature. In a series of 13,676 African American and white Medicare beneficiaries with either managed care or fee-for-service insurance, the magnitude of ‘racial’ disparity in influenza vaccination versus fee-for-service was compared. The investigators reported that the magnitude in ‘racial’ disparity in vaccination was statistically significant in both groups, although overall the rates for managed-care enrollees receiving influenza vaccination were higher.25 Thus, even if universal health coverage began next month in the United States, there are additional qualitative issues that need to be addressed before disparities in health care will be mollified.

Surgical rates of intervention: is there a difference?

Attitudes of physicians towards patients may be influenced by the status of their health coverage. In a survey of practicing physicians, 31% admitted not offering
patients useful services due to the perceived lack of insurance coverage for these services. Moreover, approximately a third of the physicians who responded to the survey reported making this judgment more often now, compared to five years ago. In the glaucoma literature, there is evidence that among Medicare enrollees self-reported African Americans underwent laser trabeculoplasty and trabeculectomies at half the rate of the whites between 1991 and 1994. These findings corroborated an earlier report by Javitt and coworkers, who noted an observed rate of glaucoma surgery among blacks that was 45% lower than the expected rate among Medicare enrollees between 1986-1988. Thus, the higher rates of blindness due to glaucoma reported among blacks may in part be due to nonbiological factors.

**Ethnic-specific therapy: does it exist?**

The debate regarding the potential existence of ‘race-specific’ drugs is one that has captured the attention of the medical profession in recent years. For example, the literature suggests the existence of population differences in the response rates to medications used to treat systemic hypertension and depression. However, Jorde and Wooding in a recent review article opine that reliance on population affiliation to determine responsiveness to therapy may be faulty. Since disease or therapeutically-predictive alleles require only a few genes as evidenced by the apparent significance of any clinical observation, the involved genes are likely very ancient and thus commonly seen across populations. An example is the gene which codes for angiotensinogen (AGT), which is associated with an elevated risk of developing systemic hypertension. This variant can be found in as many as 90% of some African populations and in at least 30% of European populations. Thus, there is enough allelic variation in this gene to warrant careful screening of individuals rather than making assumptions based on an affiliation with a specific population.

When considering the treatment of glaucoma, there have been claims that either specific drugs or treatment algorithms may be more effective in some groups versus others. With regard to the former, the prostaglandin analog, travoprost has been touted as being more effective in self-reported African American versus others. Consider the evidence for this claim. A post-hoc analysis of a subset of 801 patients who were randomized to either two different concentrations of travoprost, 0.0015% versus 0.004%, timolol 0.5%, or latanoprost 0.005%, was performed. The analysis was based on 45 and 49 African Americans in each of the travoprost groups, 40 in the timolol 0.5% group, and 43 in the latanoprost group. The investigators reported that black patients evidenced lower intraocular pressure following treatment with travoprost 0.004% (16.7 to 18.4 mmHg) compared to latanoprost 0.005% (18.0 to 19.7 mmHg). The difference in IOP was statistically different. However, there was a difference in baseline that was not addressed by the authors. Those self-reported African Americans in the travoprost 0.004% group evidenced lower intraocular pressures at baseline compared to the latanoprost 0.005% group, which may have affected the reduction in intraocular pressure that was ultimately measured. The authors alluded to a ‘racial’ basis for the discrepancy. In two subsequent prospective, randomized trials, Netland and coworkers assessed the comparative efficacy of travoprost in black and white patients. One study, involving 787 patients, was a 12-month trial, that compared two different concentrations of
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Travoprost, 0.0015% and 0.004% qd, latanoprost 0.005% qd, and timolol 0.5% bid. Pachymetry was performed in this study, however there was not a statistically significant difference (p = 0.06) between the central corneal thickness measurements among blacks (553 ± 45 um) and others (567 ± 45 um). In this study, baseline IOP was not significantly different, and the mean IOP was noted to be significantly lower in black patients than others at the 10 AM time point throughout the study when comparing those black patients randomized to travoprost 0.004% (n = 48) to others (n = 147). When adjustments were made for sex, age, iris color, diagnosis, and corneal thickness, this statistical difference persisted. Moreover, when a comparison was made between travoprost 0.004% and latanoprost 0.005%, travoprost 0.004% reduced the IOP more significantly across all time points, i.e. 8 AM, 10 AM, and 4 PM. In another six-month study which compared travoprost either 0.0015% or 0.004% and timolol 0.5%, travoprost 0.004% reduced IOP significantly more in blacks compared to others at only one 10 AM time point throughout the study.

Although two of these studies suggest there may be a difference in the response of blacks to travoprost 0.004% compared to others, it is important to consider the data from other perspectives. Central corneal thickness, for example has been shown to influence the efficacy of medication. However, this measurable biological characteristic was not significantly different between blacks and others who were involved in the study in which it was measured. Thus, this potential contributor to this observation requires further study. Furthermore, there is no evidence that topical protaglandins bind to synthetic melanin. Thus, it is not surprising that the iris color did not influence the response. Interestingly, latanoprost was noted to demonstrate a greater IOP reducing effect in Mexican and Asian clinical studies, compared to other studies including African Americans, and Caucasians. However, there is no claim that latanoprost is the drug of choice for these populations. Moreover, the analysis was controlled for age, sex, baseline IOP, previous medical therapy, and ocular diagnosis. Corneal thickness was not measured in these studies which involved latanoprost.

There are likely many contributors to the observed responsiveness to any given medication. Some of these factors have yet to be identified. These contributors are not necessarily segregated in large population groups, given the significant genetic variation that exists within populations. Since a gene that predicts responsiveness to F-Prostaglandin receptor-mediated drugs has not yet been identified, the practice of considering a drug to be particularly effective in a specific ethnic group should be discouraged.

The Advanced Glaucoma Intervention Study noted a difference in the treatment algorithm for blacks versus whites. Essentially, patients were randomized to either argon laser trabeculoplasty or trabeculectomy following failure to control their disease with maximal medical therapy. If the first intervention failed, then patients underwent either trabeculectomy (following trabeculoplasty) or trabeculoplasty (following trabeculectomy). Both groups received as a potential last intervention, trabeculectomy, if necessary. The self-reported African Americans in the trial evidenced better outcomes when argon laser trabeculoplasty was the first surgical intervention versus trabeculectomy compared to other patients who underwent trabeculectomy as an initial intervention. The authors offer a compelling basis for their conclusion; however, it is important to consider these findings from a different perspective. Since the African Americans were on more medications prior to their intervention compared to others, perhaps the medical therapy may have
influenced their poorer outcome following trabeculectomy versus trabeculoplasty. Studies suggest that topical medications such as pilocarpine and epinephrine may influence the outcome of filtration surgery. Also, clinically, the duration of treatment can also influence the spectrum of cells found in the conjunctiva. Thus, it would be important to know if a reanalysis of the data based on number of drugs, concentration of cholinergic therapy, and duration of therapy may result in a similar result, i.e. differences between two treatment algorithms.

The author realizes that this paper has raised more questions than provided answers. However, as stated in the introduction, there was an acknowledgement that these are difficult questions. With regard to sex and its influence on glaucoma, there is likely an influence when considering low tension glaucoma and angle closure. Ethnicity is more challenging, since socioeconomic factors among other factors may play a more significant role. Specific biological factors such as age, central corneal thickness, large cup to disc ratio are key risk factors. Not surprisingly, ‘race’ did not prove to be a risk factor in the Ocular Hypertension Treatment Study, when these previously mentioned factors were accounted for in the analy-

Fig. 2. This figure illustrates the genetic diversity that exists among African populations (below), which is as significant as other populations located elsewhere in the world. (Published with permission of Nature Genetics)
Does either sex or ethnicity matter in glaucoma? Given that patients who are considered ‘African American’ are recent offspring from the most diverse genetic pool in the world, it is apparent that a single, over-simplified characterization is not sufficient (Fig. 2 highlights the genetic diversity that exists among African populations). Thus, clinicians should strive to individualize their approach to patients, consider each patient’s own family history, and avoid the pitfall of relying solely on data derived from large groups of individuals who may have limited relevance.

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Low tension glaucoma: A bad concept that just won’t die.
So how do you deal with it?

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Drive a stake in its heart? Will that be the only way to kill the myth of Low Tension or Normal Tension Glaucoma? One of the great mistakes of ophthalmic history is the idea that those with open-angle glaucoma (OAG) who have normal intraocular pressure (IOP) are somehow different, have a different course, or really are not the same as other OAG patients. How did we get into this mess?

For many decades, in the era prior to disc photography, quantitative visual field testing, and epidemiological studies, the idea arose that OAG was the disease of ‘elevated’ IOP. Clearly, then, anyone who had something that looked like OAG, but had normal IOP was weird and should undergo neurological evaluation, imaging, and be told that they were going blind and there was nothing we could do for them.

Then, a series of population-based studies of persons with typical disc and field damage for OAG was performed. The investigators were surprised to find that half of those with OAG damage at the optic nerve had IOP measurements that were within the normal range. As the most modern studies have been done of those developing OAG under observation in populations, over half develop OAG without benefit of an IOP above the former magic number\(^1\)\(^2\) (which will not be mentioned in this paper). It is true that, on average, OAG patients have higher IOP than the non-glaucoma population. But, many of them never have ‘elevated’ IOP. We must simply rid ourselves of the prejudice that OAG must be associated with high IOP.

The new definition of OAG describes the disease as an abnormality of the optic nerve with typical cup and field findings. It has no level of IOP that defines the disease.\(^1\) The optic disc excavation that differentiates OAG from other optic nerve diseases has been repeatedly shown to involve a deepening of the lamina cribrosa opening at the disc that differs dramatically from neurological injury to the optic nerve, including that seen in disorders such as ischemic optic neuropathy.\(^2\) Simple loss of retinal ganglion cells, as seen in primary optic atrophies, causes the surface...
of the disc to subside backward somewhat, and the whole disc becomes pale. In OAG, the central portion of the cup is deeply placed, but the remaining rim is pink.

It is actually quite rare to find a clinical example of conditions that look like OAG but are due to some other disorder. The clues to this situation are that those that are not OAG have:

- Pallor of the disc rim out of proportion to the degree of cup enlargement
- Field defects that do not match the asymmetry of the disc rim loss
- Central visual defects (acuity and color vision loss) prior to end-stage field loss
- Field findings that are homonymous or respect the vertical midline
- Rapidly progressive course

So, if low tension glaucoma is so common, why do people consider it to be rare? We clinicians live in an insulated world, seeing what is referred or self-referred to us. Those with higher IOP come from many sources, due to pressure screening systems. Those with normal pressures only come to attention when someone notes their disc is excavated, or the patient complains bitterly about losing central vision. Once we begin to count up the times we see OAG at normal IOP, we realize that it is quite common and commonplace to deal with.

Should we do cerebral imaging on those with normal tension OAG? This question, which I have been asked at every meeting at which OAG is discussed for twenty years, is a very important one. The answer is: if you are going to image normal tension glaucoma, then image high tension glaucoma. You have the same chance to find a brain tumor in both groups. Because they have the same disease. But, if the picture fits one of the non-glaucoma criteria listed above (the disc and field do not fit, the central vision is affected) then do the imaging. But, be aware that the patient who is sent for brain imaging will never forget the terror of being told he/she may have a brain tumor. And, an extraordinary number of imaging studies are read as showing ‘minimal atrophy due to vascular disease’ or ‘lucencies compatible with multiple sclerosis’. Over-reading of imaging studies is a cottage industry and is a permanent memory for any patient. We should not affect the quality of life of persons with a treatable disorder in the mistaken search for something they do not have.

Should studies that examine OAG divide patients into those with ‘low tension’? By dichotomizing OAG into two ‘groups’, researchers degrade the quality of their projects, and actually make it less likely that they will derive useful information. It has been often reported that there are ‘vascular’ abnormalities in low tension patients. But, it is equally likely (perhaps more so) that vascular phenomena are important as risk factors in higher pressure OAG as well. Studies that examine this issue should not cut the sample size of the study in half by looking only at those with normal IOP. The evaluation should be done by including all OAG patients and treating IOP as a continuous variable, which maximizes the determination of an IOP-dependent association with the factor of interest.

Al Sommer wrote: “If there is no such thing as an abnormal pressure, only pressures at which the risk of glaucomatous optic nerve damage is higher or lower than average, then there is no basis for the term low-tension glaucoma.” M. Roy Wilson wrote: “With respect to normal tension glaucoma, there is no such disease entity – distinct from primary open angle glaucoma – and it serves no useful purpose to continue to perpetuate this term.” How long will it be before
Low tension glaucoma

the correct concept of OAG and its relation to IOP is translated from the known scientific facts into appropriate clinical behavior?

References

Neuroprotection strategies from the research lab (‘cause there aren’t any ready for prime time yet)

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We now know that open-angle glaucoma (OAG) happens at all intraocular pressure (IOP) levels. Thus, it is irrational to believe that the treatment should be to ‘normalize’ the IOP or to lower IOP below 21 as the goal of treatment.1 If we operationalize the concept that glaucoma happens at any IOP, then we should determine in each patient an average baseline untreated IOP. From this level, IOP-lowering will occur. There is good evidence from recent clinical trials2,3 that lowering of IOP by 20-30% decreases progressive worsening in OAG by 50-60%. So, we have already got a means of neuroprotection, namely, lowering IOP.

It is logical that the target pressure should be lower when there is substantial damage already present in the visual field.4 But, how much should IOP go down? Some advocate decreasing it to 12 mmHg or less based on some clinical trials data. But, there must surely be a risk/benefit ratio associated with such lowered IOP and the treatments needed to get there. Furthermore, it makes no more sense to lower everyone to 12 than it did to use 21 as a magic number. So, the next steps in needed research are to determine the relative efficacy of various levels of IOP lowering adjusted for the variety of clinical pictures that present themselves in clinical practice. To some degree, this could be approached by new clinical trials in which two or more levels of target pressure are randomly assigned to the treated OAG patients – for example, 20% versus 40% lowering.

However, the ideal approach would be to tailor the target to the risk level of the individual patient. To do so, we would need risk calculations based on the known factors of each patient, and recalculated over time as new IOP, disc, field and other information revealed itself during follow-up. This should be a goal for us all.

Some portion of glaucoma injury is surely independent of the prevailing IOP and its fluctuations. To attack this area requires a different approach. If we examine the process of retinal ganglion cell (RGC) injury and death in glaucoma, there are clues about how new preventive strategies might be developed to preserve the
maximum visual function and quality of life for OAG patients. In both experimental models and human eyes with glaucoma, RGC axons at the optic nerve head show anatomic and physiologic injury. The death of RGC was found to occur through apoptosis, the reactivation of a programmed sequence of cell suicide. A logical link between these two facts would be to suppose that axonal transport blockade from the injury to RGC fibers at the nerve head produced an obstruction in a vital messenger molecule that would normally arrive back at the cell body in the retina by retrograde movement. This fall in messenger would initiate apoptosis. In embryological life, RGC know that they are properly paired with their brain center partners by receiving the appropriate messenger molecules from the brain. When they are misdirected and fail to reach the right target, the fall in messenger level leads to cell death. We proposed that this process repeats itself in adult life by the injury of glaucoma – in effect, pathology recapitulates ontogeny.

Indeed, the important messenger protein, brain-derived neurotrophic factor, is blocked from coming from the brain to the eye at the nerve head in experimental glaucoma. When it is provided to RGC by gene therapy in experimental glaucoma, a substantially lower number of RGC die, without lowering of IOP. This, then, is a potential neuroprotective therapy area. Whether the neurotrophin would be delivered by gene insertion, by injected cells carrying the gene and chronically expressing it, or by pharmacological delivery remains for further research.

In such clinical trials, non-IOP treatments that will be tested in humans will be entered in protocols that consist of large numbers of patients, all of whom will have some IOP lowering, and the neuroprotective agent will be tested in half of the sample for its additional benefit in slowing structural or functional loss.

Another gene therapy success was reported by McKinnon et al., when they inserted a gene that blocks a late stage of enzyme activation in the apoptosis process, again in the rat glaucoma model. Any method that prevents RGC death and preserves their function would be a welcome addition to our armamentarium. However, it makes sense to attempt to interrupt the process as early as possible in the cascade of pathological events.

Some early events occur at the interface between the RGC axon and its supportive and nutritional tissues in the nerve head. The level of IOP is transmitted to RGC by the corneoscleral shell, most critically the collagen and elastin containing connective tissues of the nerve head. Failure to retain normal elasticity could be an initial link between IOP and RGC injury. In order to recognize that axonal shape is being altered by external forces, pressure sensitive channels (TRAAK channels) may be the operative pathway. RGC axons might be made less sensitive to compression through manipulation of TRAAK channel sensitivity.

A molecule that deserves study is the motor protein that carries messenger proteins on their receptors is dynein, a huge complex riding along the axonal microtubules. It requires substantial ATP-provided energy to bring messengers back to the RGC body, and may be the nexus for action of failure in nutritional blood flow to the axons. Each of these ‘upstream’ areas deserves intense investigation for protective interventions.

Finally, there are a variety of other pieces of evidence linking various processes to RGC death in glaucoma. Free radical damage mediated either through nitric oxide synthesis or glutamate excitotoxicity has been suggested as events that may serve as therapeutic avenues.
Neuroprotection strategies from the research lab

Stimulation of immune-mediated phenomena by glatiramer has also been suggested to improve outcomes in experimental glaucoma. It is not clear how nitric oxide or glutamate toxicity relate to the other risk factors for glaucoma, or how they fit into the pathway from initial events to RGC death.

It is possible that some RGC die from primary injury and that others are killed by secondary events initiated by the primary deaths. We may, then, be looking for neuroprotective approaches that block events in the IOP-initiated pathway or events that result from the disturbed environment produced in the retina and optic nerve by initial glaucoma damage that are IOP-independent.

Future of glaucoma therapy will come from our new ideas and research, if we are prescient enough to ask the right questions and test them rigorously.

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The myth of the glaucoma continuum

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Introduction

According to Webster’s Dictionary, a myth is “a traditional story […] that serves to […] explain a practice, belief or natural phenomenon”, or something “having only an unverifiable existence”, or “an ill-founded belief held uncritically, especially by an interested group”.

I contend that just such a myth has developed around the belief that structural damage to the optic nerve always precedes functional loss. It began with several papers, published in the 1970’s, reporting that structural damage of the optic disc generally preceded visual field loss as detected by the Goldmann Kinetic Perimetry.1-4 A mythical paradigm was adopted by many that this was always so.

The paradigm was updated by Quigley and then Weinreb with quantitative methods. Quigley and coworkers counted optic nerve fibers in autopsy specimens and correlated the results with the most recent Goldmann kinetic visual fields obtained before death, concluding that “Patients may lose up to 40% of their optic nerve fibers before damage can be detected” and “Patients may lose up to 90% of their nerve fibers before they notice symptoms.”5 Weinreb and coworkers compared the results of optic nerve imaging to automated visual field testing, concluded that structural changes usually precede functional changes by several years, and proposed the ‘Glaucoma Continuum’ (Fig. 1).6

According to the diagram of the Glaucoma Continuum, ganglion cell death precedes detectable retinal nerve fiber loss, which precedes loss detectable by selective functional testing such as Short Wavelength Automated Perimetry (SWAP), which precedes visual field loss detected by Standard Automated Perimetry (SAP) and finally blindness. The way the diagram represents the process, damage is already quite advanced before visual field loss is detectable. To be fair, the authors acknowledge that functional loss sometimes is detected before structural loss, and that both must be assessed, but the diagram ignores that possibility.

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The consequences of adopting the glaucoma continuum

The widespread advocacy of the Glaucoma Continuum has had important consequences. It brought proper attention to looking for structural changes, which is certainly appropriate – a big plus. However, the misleading aspects of the diagram have been taken too literally by some ophthalmologists, leading to an inappropriate aggressiveness with medication and even surgery to treat ocular hypertension in the absence of either visual field or disc changes, for fear of ‘losing half of the optic nerve’ before field loss develops and an additional fear that ‘once damage occurs it is difficult to halt progression’.

It ain’t necessarily so

What is the current evidence regarding the validity of the dictum that structural change precedes functional change? There have been three modern tests of the hypothesis.

First, in the Ocular Hypertension Treatment Study (OHTS), damage was first detected by masked reading of serial stereophotography of the disc in 55% of cases, but first by confirmed visual field loss in 35% and both in 10% (Fig. 2). The earlier detection by disc change may in part be an artifact of the protocol, which required change on three visual fields over 12 months, whereas disc change could be confirmed on two examinations over 6 months. We will have to await further analysis of the OHTS results to clarify this. A more appropriate analysis would be to attribute the date of change to the first observation of a subsequently confirmed change.
A second test of the hypothesis was performed by Artes and Chauhan, who used Heidelberg Retinal Tomography (HRT) to detect changes in structure and both SAP and High-Pass Resolution Perimetry to follow function, and reported that change was detected first by structure two-thirds of the time and by function one-third of the time. There was little correlation of structural change and functional change at the first sign of change, as in the OHTS. The authors suggested that perhaps redundancy in receptor fields hides the initial loss of function, while perhaps sick cells malfunction without as yet dying.

The third test of the hypothesis was a widely misinterpreted study, in which Harwerth taught monkeys to do SAP and then created glaucoma with laser ablation of the trabecular meshwork. Monkeys were sacrificed at various stages of damage and the ganglion cell density and visual field loss were determined in corresponding areas of the retina (Fig. 3).

The curve relating visual field sensitivity loss to the percent of ganglion cell loss was fairly flat with early cell loss, and then rose progressively with moderate to severe loss. This has been widely misinterpreted to mean that the first 50% of cell loss occurs with little loss of visual field, but in fact, just the opposite is true. What is generally missed is that the intercept on the visual field loss axis is at 6 dB, not 0 dB, and means that there was a quite significant loss of visual field sensitivity from the beginning in this model in which the intraocular pressure was raised abruptly, and that the flat portion of the curve represents the death of cells that had already lost their function. So, in this model, loss of function preceded loss of structure.
Fig. 3. The correlation of ganglion cell loss to VF loss in Harwerth’s monkeys. In this acute model of glaucoma a 6 dB depression of field preceded cell loss, not a 50% loss of cells before a loss of function.

Alleviating fear about loss of a substantial portion of the optic nerve before loss is detected, or that once field loss is present that progression would be difficult to halt

With the use of Optical Coherence Tomography, it is unlikely that more than 20% of optic nerve fibers would be lost without the loss being detected, and rarely is more than 25-30% thinning of the retinal nerve fiber layer noted by OCT without corresponding loss on SAP. Furthermore, the Collaborative Initial Glaucoma Treatment Study (CIGTS) demonstrated that with aggressive lowering of IOP (35%) no net visual field loss occurred in 5 years in initially diagnosed cases. The Advanced Glaucoma Intervention Study (AGIS) demonstrated that with lowering of IOP to the low normal range no net visual field progression occurred in 8 years. There is no need to be overly aggressive when no detectable functional loss is present.

Future Studies of Structure and Function in Glaucoma

Improvements in our ability to measure both structure and function in glaucoma are currently undergoing validation. The newest versions of Optical Coherence Tomography (OCT) have been shown to have a 3 micron-resolution, far outperforming current HRT, OCT and Laser Polarimetry. Improved tests of function include SWAP and Frequency Doubling Technology (FDT), which have the advantage of isolating the function of sub-groups of retinal ganglion cells, and the Pattern Visual Evoked Potential (PVEP) and the Pattern-Electroretinogram (PERG). The latter two may be compared to a stress electrocardiogram, in that the retina is
exposed to rapidly alternating black and white stripes, presumably stressing the metabolic ability of the retinal ganglion cells to fire repeatedly. The PERG test has demonstrated a reversible loss of function in some ocular hypertensives in whom no structural loss (by OCT) or conventional functional loss (by SAP) is detected. The depression of the PERG amplitude reverted to normal in several subjects in whom the pressure was lowered medically, with a time course of several days to a few weeks. Such reversal might be a sign of adequate IOP control, suggesting the use of PERG as an ‘axon screamometer’, useful in determining an appropriate target pressure for an individual.

Conclusions

The myth of the Glaucoma Continuum as it is sometimes presented has overstated the case for structural change preceding functional change. Functional changes can occur before structural ones, especially with recent, acute IOP changes. While the stress on monitoring structure has been constructive, it should not cause us to ignore monitoring function. Furthermore, with current methods of monitoring optic nerve structure and function, no more than a quarter of the tissue is likely to be lost before we can detect it, and clinical studies show conclusively that glaucoma damage can be halted in the great majority of cases with adequate treatment. Therefore, there is no need to fear that glaucoma damage once started would be difficult to stop, nor to be overly aggressive in trying to prevent the first detectable damage.

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Landmark clinical trials in glaucoma: Questions and answers

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Introduction

Over the past two decades, several clinical trials in glaucoma have provided support for IOP lowering therapy for both ocular hypertensive and primary open angle glaucoma patients that was lacking in prior generations. No clinical trial is perfect and the impact and limitations of these studies should be kept in mind when incorporating the recommendations of study investigators into clinical practice.1,2

Under the best of circumstances, there is no more powerful study design than the prospective randomized multicenter clinical trial. Such studies provide the highest quality of evidence in support of, or against, a particular hypothesis evaluating new or existing therapy.1 Randomized clinical trial results are often considered ‘credible’, even when there are limitations in the study hypothesis, design, conduct and interpretation. Such studies form the cornerstone for ‘evidence based medicine’, which is a concept that is increasingly considered important in guiding virtually every treatment decision. While some and perhaps the majority of practitioners believe that our glaucoma practice patterns in the 21st century are more ‘precise’ or ‘evidence based’ than those of our predecessors, the benefit to our patients from these studies has been limited and is open to debate. Further, the potential for systematic error or misinterpretation is certainly not eliminated when one conducts a randomized clinical trial.2

One way to look at a randomized clinical trial is to evaluate the quality of the question that was asked and whether or not that question was adequately answered. Another equally important issue relates to the types of patients that were included in each of the studies. For example, in the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS), patients had above average IOPs but did not have glaucoma.3,4 On the other end of the spectrum, the average patient in both the Advanced Glaucoma Intervention Study (AGIS) and the Collaborative Normal Tension Glaucoma Study (CNTGS)
had at least moderately advanced disease, with patients in AGIS having relatively high IOPs on maximal medical therapy while those in CNTGS had relatively lower IOPs. In the middle of the spectrum with regard to disease severity were the patients in the Collaborative Initial Glaucoma Treatment Study (CIGTS) and the Early Manifest Glaucoma Trial (EMGT). Both of these studies enrolled patients who had early manifest glaucoma or newly diagnosed glaucoma (possibly intermediate stage). The average IOP was higher in CIGTS patients than in patients who were enrolled in EMGT. All of these trials had different treatment goals. For example, while the treatment goal for patients in OHTS was a 20% reduction in IOP, it was 30% in CNTGS. EMGT and EGPS had no IOP goals in the treated group. The patients received a therapeutic regimen and regardless of the extent of IOP lowering, the treatment was not adjusted. In CIGTS, the IOP target was determined by a formula using both visual fields and the level of IOP when patients entered the study. Finally, in AGIS, the goal of treatment was an IOP lower than 18 mmHg at all time points regardless of the level at which the patient entered the study.

CNTGS

The key question asked in CNTGS was: is IOP-lowering therapy appropriate in patients with normal-tension glaucoma? Prior to this study, there was doubt regarding whether or not therapy should be initiated in glaucoma patients with IOP in the normal range. While occasional IOPs of up to 24 mmHg were allowed, the majority of patients had all IOP readings below 21 mmHg. One eye of 145 subjects was randomized to treatment or observation and all eyes were treated if either progression was noted or fixation threatened. The treated group achieved a 30% reduction in IOP using medications, laser and surgery. No beta-blockers or other adrenergic agents were used, largely because there was a concern that these drugs may negatively impact ocular blood flow or optic nerve blood flow resulting in further glaucomatous damage. This hypothesis has not as yet been proven. The treated group had a mean 12% risk of glaucomatous progression, whereas the untreated group had a 35% risk of progression over the follow up period. Treatment with IOP lowering therapy reduced the risk of further visual field progression in patients with normal tension glaucoma. The trade off was, that treated patients were more likely to lose vision and require surgery for cataract, compared to the untreated group. The CNTGS showed us that non-surgical therapy is effective in lowering IOP, even in patients who have average or ‘normal’ IOP. The study confirmed that IOP lowering therapy in such patients was effective in preventing glaucomatous visual field progression. While the study elucidated risk factors for progression, such as disc hemorrhage, migraine headache and female gender, it did not explain why a substantial number of patients with normal tension glaucoma did not progress, even without treatment. Prior progression was considered a risk factor for future progression. The CNTGS was the first randomized clinical trial to prove that IOP lowering therapy was effective in preventing the progression of open angle glaucoma. Ironically, this breakthrough study evaluated patients with ‘normal’ pressures. CNTGS was the first study to
Landmark clinical trials in glaucoma answer the Eddy and Billings report which had questioned the rationale for IOP lowering therapy.

AGIS

AGIS asked the question: should one perform laser trabeculoplasty or trabeculectomy first when maximal medical therapy fails? Patients treated with laser trabeculoplasty underwent trabeculectomy if IOP lowering was not adequate with such initial therapy. If the first trabeculectomy failed, patients in this group underwent a second trabeculectomy procedure. In contrast, patients randomized to the surgery first group underwent laser trabeculectomy if trabeculectomy failed and then another trabeculectomy as a last resort. This latter treatment algorithm, unlike the former, did not reflect common practice, even when the study was designed and certainly not at the time it was completed. Thus, while the hypothesis was certainly worth studying, the study design created a situation where direct treatment recommendations based upon these algorithms would have been difficult to justify.

In AGIS, 789 eyes on maximal medical therapy (three medications) were included and all patients had either an IOP of 18 to 21 mmHg with deterioration of visual fields, or 21 mmHg or greater with a sufficient amount of visual field loss to be entered into the study. The goal of treatment for all patients was to lower IOP below 18 mmHg with or without medications at all time points in the study. The answer to the initial question was not unexpected. A greater IOP reduction occurred in patients who had trabeculectomy first, laser trabeculoplasty second and then trabeculectomy again than in patients who underwent laser trabeculoplasty first with two trabeculectomies afterwards if necessary. Curiously, however, visual preservation was greater with the laser trabeculoplasty first group in African American subjects and in the surgery first group in white patients. While the initial question became progressively less interesting to many ophthalmologists as the study progressed, a significant amount of attention was turned to other analyses assessing the relationship between IOP and visual field progression. A Predictive Analysis pooled data from both surgery and laser first eyes. Eyes with lower mean IOP on the first three visits at 6 month intervals in this pooled data were less likely to progress during the course of the study. One limitation of this analysis was, of course, the fact that mean IOP could have changed in the period after the initial three visits and thus the analysis did not take into account the mean IOP throughout the study.

The post hoc analysis that received the most attention, however, was the pooled Associative Analysis in which the subgroup of patients in both treatment groups who had pressures lower than 18 mmHg at every visit throughout the study were found, on average, to have no visual field progression. This subgroup had a mean IOP of 12.3 mmHg, which was lower than the mean IOP in subgroups that had greater proportions of visits with IOP greater than 18 mmHg. Unfortunately, this led some to consider the number, 12.3 mmHg, to be somehow important in glaucoma therapy as a target goal. While lower is certainly better than higher in most cases, one should keep in mind that patients were not randomized to the
subgroups in the Predictive and Associate Analyses and thus such conclusions based upon selective data mining have to be examined with caution.

Finally, a recent analysis looking at IOP variation in the AGIS study has impacted our understanding of glaucomatous optic nerve progression. The subgroup of patients with less IOP variability was found to have a lower rate of visual field progression than the group with greater variability.13

AGIS, more than any other randomized clinical trial in glaucoma patients, focused attention on parameters other than mean IOP and their importance in predicting glaucoma progression. One must remember, however, that this attention on peak IOP and variation in IOP on different visits had little to do with the initial question of the study. Another limitation of AGIS was the fact that only a single baseline visual field was obtained at the commencement of the study. Investigators for studies that followed AGIS recognized this limitation and obtained multiple baseline visual fields.

EMGT

EMGT asked the question: should patients newly diagnosed with glaucoma be treated with IOP lowering therapy?8 One could make the argument that this question had already been answered prior to the commencement of EMGT but some felt another study was needed to confirm the benefit of treatment in such patients. One positive aspect of the study was that subjects were identified via a screening rather than using a clinic based population. It is certainly easier to discuss the possibility of randomizing to treatment versus non treatment of glaucoma with patients who are identified via a screening relative to those who have already been told that they have a problem with their eyes. Two hundred and fifty five patients who were identified from 44,243 screened individuals were randomized to either laser trabeculoplasty and betaxolol or no IOP-lowering therapy. There was no target IOP in this study and thus once patients were randomized to treatment, they received, for the most part, only the combination laser and drug therapy, regardless of whether and to what extent their IOP was lowered.

The group of patients who were treated had a 45% rate of progression, compared with a 62% rate of progression for the patients in the untreated group.14 The risk factors for progression in EMGT included higher baseline IOP, higher treated IOP, exfoliation syndrome, frequent disk hemorrhages, age and bilateral disease.

The conclusion of EMGT was that in patients newly identified as having open angle glaucoma, IOP-lowering therapy was beneficial in reducing the risk of progression. The study investigators concluded that IOP lowering therapy reduced the risk of progression by 50% and that every mmHg IOP lowering resulted in a 10% reduction in such risk.14,15 The IOP reduction in treated EMGT patients was relatively modest, with a mean lowering of 25% and a substantial proportion of patients obtaining significantly less. Thus the 1 mmHg-10% risk reduction conclusion was viewed with caution. An additional weakness of EMGT was that stereo disc photography was not used to document progression. It has long been known that in early glaucoma, the optic nerve can change without much effect on the visual field in many patients. The small number of patients that progressed based
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upon optic nerve changes alone in this study was not surprising given the method by which optic nerves were assessed.

The overall impact of EMGT on glaucoma practice was minimal as by the time the study findings were released, most ophthalmologists were already convinced that IOP lowering therapy was beneficial in preventing glaucoma. Nevertheless, EMGT addressed the questions posed by the Eddy and Billings reports more directly than any of the other studies. 8

CIGTS

CIGTS asked the question: in patients with newly diagnosed glaucoma, is initial surgical therapy preferable to initial medical therapy? 7 In the United States, initial medical therapy has been the standard with surgical options reserved for patients who continue to progress despite medications. A study in the U.K., performed in the 1980’s, showed that glaucoma patients who underwent initial trabeculectomy had better visual preservation than those undergoing initial medical therapy or laser trabeculoplasty. 16 This led to some debate throughout the world regarding which treatment option should be recommended first.

In CIGTS, 607 patients at 14 centers who were newly diagnosed with open-angle glaucoma were randomized to either initial medical therapy or initial trabeculectomy. The group of subjects that received medicine first received laser second and trabeculectomy third if target IOP was not reached. The group receiving surgery first, received laser and medicine second and third respectively as needed. This latter algorithm certainly did not represent a common practice pattern anywhere in the developed world. A target IOP was determined for each patient based upon a formula that took into account baseline visual field status and IOP. The primary outcome variable was the visual field score, but IOP, quality of life and cataract formation were also evaluated. It was found that after a five-year period, the surgery-first group had at least a 2 mmHg lower IOP at every time point than the medicine-first group. 7 This difference, however, did not translate into better visual preservation, as there was no difference in visual field scores at the five-year time point between the two groups. In addition, patients preferred initial medical therapy largely because of the ocular side effects associated with glaucoma filtration surgery.

The finding of CIGTS were somewhat contradictory to those of EMGT. The latter study suggested that every mmHg IOP lowering was important in predicting visual field progression while the former indicated that if IOP was lowered substantially (over 35% in both surgery and medicine first groups) each additional mmHg IOP lowering may not be critical. This difference in findings, once again, reinforces the importance of avoiding dogma when it comes to explaining the relationship between IOP and glaucoma progression.

CIGTS confirmed that medical therapy should continue to be the ophthalmologist’s first-line of treatment for glaucoma patients as present day medications allow substantial reductions in IOP which appear to protect the optic nerve as much as similar or even slightly greater reductions in IOP with initial surgery. One difference between CIGTS and studies performed in the 1980’s and early 1990’s relates to the quality of IOP lowering with glaucoma medications that were available at
the time these studies were undertaken. The addition of several new classes of medications in the 1990’s certainly impacted glaucoma therapy positively.

OHTS

OHTS asked the question: does IOP lowering therapy in patients with ocular hypertension decrease the risk of developing open angle glaucoma? The study included 1,636 patients at 23 centers. At five years, approximately 5% of treated patients developed open-angle glaucoma vs. approximately 10% of untreated patients. There was an approximate 5% absolute risk reduction versus an almost 50% relative risk reduction with treatment. Additionally, patients with the thinnest corneas, the most cupped optic nerves and the highest IOPs were the most likely to develop glaucoma if they did not receive IOP-lowering treatment. However, the study did not fully evaluate whether or not patients in these high risk subgroups who received treatment benefited more or less than the overall group of patients who were treated. The study also did not tell us whether treatment of ocular hypertension reduced the risk of ultimate functional vision loss from glaucoma. This latter question will be addressed in a continuation of this study.

One question that comes up in OHTS as well as other clinical trials, relates to what can be considered a risk factor for disease. By definition, patients with ocular hypertension have no visible evidence of damage to the optic nerve by structural or functional assessment. Thus one can make the argument that optic nerve and visual field parameters should not be considered risk factors for the disease. Purists will certainly argue that factors which define the disease should not be considered risk factors. For example, coronary artery occlusion is not classified as a risk factor for coronary artery disease but is rather a manifestation of the disease itself.

Surprising findings from OHTS included the lack of importance of family history as a risk factor in the study and the apparent protective effect of diabetes in preventing conversion to glaucoma. This latter finding was dismissed by many given that patients with diabetic retinopathy, presumably those with more severe disease, were not allowed into the study. One must consider, however, whether this association suggests that diabetics with well controlled disease are somehow better off than non diabetics when it comes to the likelihood of developing glaucoma. To dismiss this possibility completely based upon our preconceived notions regarding the disease processes of diabetes and glaucoma could turn out to be a mistake.

Perhaps the greatest impact of OHTS was that it led to the rapid incorporation of central corneal thickness measurement into glaucoma practice and further study in this area. One can argue that the emphasis on central corneal thickness measurement in glaucoma practice, while clearly important, has been somewhat exaggerated by the OHTS findings. Other corneal parameters, most notably elasticity, are at least equally important.
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EGPS

EGPS asked the same question as OHTS: does IOP lowering therapy in patients with ocular hypertension decrease the risk of developing open angle glaucoma? There were two major differences between EGPS and OHTS. All patients randomized to treatment in EGPS were treated with a single medication, dorzolamide dosed three times a day and therapy was not adjusted while the patients were in the study. In contrast, there were no such restrictions in OHTS where a variety of available medications were used to lower IOP at least 20%. Another difference between the studies was the fact that the control group in EGPS received placebo (dorzolamide vehicle), while OHTS, like all of the other previously mentioned studies, did not have a placebo arm.

Several findings of EGPS were surprising to some ophthalmologists, especially those who were unaware of the specifics of the study design and conduct. For instance, the placebo effect was significantly greater than expected, measuring 9.3% at six months and progressively increasing to 18.7% at five years. Similarly, there was an apparent increase in the efficacy noted with the use of dorzolamide over time with an IOP lowering of 14.5% at six months and 22.1% at five years. The authors noted that the patients who were ‘lost to follow up’ had higher mean IOP’s during the study period than those who completed the study. Given this finding, the term ‘withdrawn’ is likely to be more appropriate than ‘lost to follow up’. Over 30% of patients who entered EGPS did not complete the study. Even partially correcting for this finding with the last observation carried forward analysis, it was found that the placebo group showed an IOP lowering of 8.6% and 13.7% at six months and five years respectively. While the approximately 1 mmHg greater IOP lowering in the dorzolamide group relative to the placebo group was found to be statistically significant as would be expected with a study of this size, the clinical importance of this greater IOP lowering with dorzolamide was not validated in that there was no statistically significant difference in the likelihood of developing glaucoma between the two groups.

The findings of EGPS contradicted those of OHTS in that the latter clearly showed a benefit of IOP lowering therapy in patients with ocular hypertension over a five-year period. Both studies recruited patients with normal optic nerves and visual fields who had higher than average IOP measured by applanation tonometry. It is noteworthy, however, that the mean baseline IOP of patients recruited to EGPS, 23.4 and 23.5 mmHg in the dorzolamide and placebo groups respectively, was lower than the minimal IOP needed for patients to be eligible for recruitment into OHTS: 24 mmHg. The mean central corneal thickness in a sample of 80% of EGPS patients was over 570 microns. While there is no validated conversion formula which corrects IOP for central corneal thickness, it is possible that not only were the optic nerves and visual fields of EGPS patients normal, the corrected mean IOP in both the dorzolamide and placebo groups may have been within two standard deviations of the mean IOP previously found in ‘normal’ caucasian populations (i.e., less than 21 mmHg). The average EGPS patient may not appropriately represent the average ocular hypertensive patient in most practices. Another potential systematic error that could conceivably account for the large placebo effect noted in EGPS is ‘regression to the mean’. Since only two IOP readings of at least 22 mmHg were required to be eligible for the study, patients who commonly had IOP readings under 22 mmHg with only occasional
readings above 22 mmHg may have been enrolled in the study. Ironically, there is overlap in the IOP criteria for entry into EGPS and CNTGS. It is impossible to assess the magnitude and significance of this possible ‘regression to the mean’ effect which can occur in all studies where a threshold IOP is required for entry.

There are a few other differences between EGPS and OHTS that should be noted. The minimal age for entry into EGPS and OHTS was 30 and 40 years respectively. OHTS had a sample size which was approximately 30% larger than EGPS and the latter study had a substantially lower completion rate amongst those who were enrolled. It is possible but cannot be stated with any certainty, that the average EGPS patient had less risk of developing glaucoma than the average OHTS patient. In general, the less significant the disease or risk of developing the disease, the less likely it is that a study will show a benefit of treatment with a drug relative to placebo.

The fact that dorzolamide use has long been recognized as being less effective in reducing IOP relative to other more potent glaucoma monotherapeutic choices such as prostaglandins cannot be discounted. Topical carbonic anhydrase inhibitors are rarely used as first line therapy for patients with ocular hypertension or primary open angle glaucoma but are commonly employed as adjunctive agents. The three times a day dosing used with topical carbonic anhydrase inhibitors when used as monotherapy can be cumbersome to patients. If one of the more commonly used first line glaucoma therapeutic agents such as a prostaglandin had been used in the treatment group, it is likely that IOP lowering would have been greater and the benefit of IOP lowering therapy relative to placebo may have been confirmed. Limiting treatment of ocular hypertension patients to one medication, regardless of the response, however, does not reflect common practice.

The design and conduct of the EGPS are critically evaluated, the findings are not particularly surprising. What is surprising, however, is the comment made by the authors of EGPS that our profession should ‘evaluate or re-evaluate’ the efficacy of long-term medical therapy of ocular hypertension and primary open angle glaucoma with placebo controlled clinical trials. While a placebo effect has long been recognized in virtually all areas of medicine, the findings of the large clinical trials that have confirmed the benefit of IOP lowering therapy in the treatment of patients at all stages along the continuum of glaucomatous disease should not be ignored simply because they were not placebo controlled. The placebo effect in EGPS is exaggerated, most likely due to some combination of selective dropout of patients with higher IOP and ‘regression to the mean’ effects. A six-month placebo effect of slightly less than 10% may be real. There is no good reason, however, to expect this effect to double over a five-year period. In contrast, the benefit of IOP lowering with medical therapy is understated in EGPS by the use of a single therapeutic agent that is not ideal for stand alone monotherapy. This combination of overestimation of the placebo effect and less than ideal treatment in the medication group has led to conclusions and recommendations from the EGPS investigators that are difficult to accept.

Conclusions

The large glaucoma clinical trials that have been conducted over the past decade, have certainly provided answers to several questions ophthalmologists are faced
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with on a daily basis. AGIS and the CNTGS showed that lowering IOP, both in patients with elevated IOP and normal IOP, decreases the likelihood of visual field loss. The post hoc analyses of AGIS revealed, to some extent, the importance of preventing IOP peaks and variation between visits in minimizing the risk of glaucoma progression. CIGTS and EMGTS had somewhat conflicting findings about the relative importance of every mmHg IOP lowering with the former study confirming that initial medical therapy is the best choice for most patients who present with open-angle glaucoma. OHTS revealed that lowering IOP reduces the risk of conversion to glaucoma and also pointed out that central corneal thickness measurements should be routinely obtained in patients with ocular hypertension, and perhaps all patients in a glaucoma practice. EGPS reminded us of the placebo effect but perhaps overstated the size of this effect based upon several limitations in study design and conduct. Overall, these studies certainly advanced our profession. Nevertheless, one must approach several of the interpretations and recommendations of study investigators with skepticism.

Randomized clinical trials vary with regard to how they are conducted and analyzed. All epidemiologic studies are prone to error and systematic or non random error is referred to as bias. One common source of bias in randomized clinical trials occurs when there is unmasking of subjects, data collectors or data analysts. Bias can also occur in the evaluation of study results. Such bias on the part of data analyzers can be diminished by prospectively agreeing on the endpoints of the study and the statistical tests that will be used to determine whether or not these endpoints are reached. Shifting baselines and post hoc analyses are commonly associated with bias, especially if the latter is undertaken by individuals who have a stake in the outcome of the study. Bias is often impossible to determine and thus the potential for bias should be sufficient to question the study results. All other things being equal, the randomized clinical trial is less likely to be associated with bias than other lesser prospective and retrospective study designs. Nevertheless, a healthy skepticism in evaluating randomized clinical trials is not only important, but necessary for good patient care.

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Practical implications of the Collaborative Normal Tension Glaucoma Study

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The Collaborative Normal Tension Glaucoma Study (CNTGS) was unique in that it was not a National Eye Institute-sponsored megastudy. Rather, it was the product of discussions held in the early 1980’s, initiated by the Glaucoma Research Foundation, Dr. Robert Shaffer’s group, and two visionaries of glaucoma of the time, Douglas Anderson and Stephen Drance. A group convened in California to ask what questions would be important to answer about glaucoma. We decided that the fundamental question needing to be answered was: “Does lowering intraocular pressure (IOP) benefit the progress of open-angle glaucoma (OAG)?” To deal with this question, a treated and an untreated group would be followed with detailed disc and field testing under rigorous conditions. The tenor of the time was such that no one could envision approval for a study in which therapy was withheld from those with high IOP. Hence, we risked the protocol on those with OAG in the range of normal IOP, never higher than 24 mmHg and routinely under 20 mmHg on no medication on 10 measurements. Even the contemplation of no therapy for persons with OAG damage at any IOP was considered fringe behavior.

It was decided that all persons to be entered into the trial would have defined OAG damage in the disc and field, and would be followed until they actually worsened by field criteria. Then, they would be randomized to either 30% IOP lowering, or continued follow-up without therapy. Exceptions were made for those with field defects close to fixation, who could be randomized immediately. The IOP was to be lowered by eyedrops (excluding beta blockers, which some felt were bad for blood flow), laser angle treatment, or surgery. We thought that it was likely that most patients would require surgery to achieve their target IOP (the concept of target IOP was not even in the lexicon at the time, but was essentially invented for this trial).

A large number of volunteer offices participated, paying for their costs in the study to learn the answer. Of 230 participant patients who entered, 140 ultimately...
showed evidence of progression. The amazing thing (to some) was that 90 patients of the original cohort showed no progression over the nearly 10 years of participation.\(^1\,^2\) It had been axiomatic that all OAG patients, and certainly the dread ‘low tension’ type, would get dramatically worse. We have since learned that the general progression rate in OAG is much more modest that originally believed. Second, many patients achieved their target (typically in the range of 12 mmHg from a baseline of 16) with drops and laser. Only 43% needed trabeculectomy surgery.

The average age of those in the trial was 66 years, the mean deviation at baseline was -5.8 dB. Overall, the relatively slow pace of OAG was determined in detail for the first time. Of those followed without any therapy, only 7% of eyes per year of the study met the criteria for field progression, which required 5 or even 6 fields to confirm change. This may seem excessive, but this study defined progression strictly due to determining early in the study that field progression often did not remain when later fields were done. Too many persons met a flimsy progression standard, only to return to the original field status by the third or fourth field. This is a major lesson of OAG management, and has been confirmed in other clinical trials. When in doubt, do another field before concluding that there is progressive change. The results of two other studies of OAG followed without therapy are in the range of the CNTGS estimate of change per year. The Early Manifest Glaucoma Trial (EMGT)\(^3\,^4\) found 10% per year of untreated OAG eyes worsened, using more sensitive (and less specific) criteria. The natural history of OAG patients in the island of St. Lucia\(^5\) indicated a 5%/year worsening rate.

Among persons treated for OAG in CNTGS, 3.6% per year became worse. When the effect of cataract on the visual field was taken into account, this was a 60% reduction in the worsening compared to untreated eyes. Furthermore, several other studies carried out since that time have generated an average worsening rate for treated OAG that is nearly identical to that found in CNTGS. From a high in the EMGT of 7.5%/year, the other studies treated worsening rates are: Advanced Glaucoma Intervention Study (4.4%/year),\(^6\) Glaucoma Laser Trial (3.7%/year),\(^7\) Wilmer Institute Clinical Series (4%/year),\(^8\) and Collaborative Initial Glaucoma Study (0%/year).\(^9\) We can conclude that patients treated by the target pressure approaches taken in these studies, under relatively ideal conditions of treatment availability and low loss to follow-up, have a slowly progressive disease. Given the average length of OAG from initial field loss to actuarial death, this means the typical OAG patient, treated ideally, does not suffer a loss of quality of life.

Indeed, the average patient in CNTGS lost only 0.1 dB per year in field sensitivity, or about 2 dB in the lifetime of their OAG. This is not trivial, since 3 dB is a 50% loss of sensitivity (rememer it is a log scale), but this sensitivity loss is easily compatible with continued normality of function in most persons. It is also not reported to be associated with a loss in functionality by patients in standardized instruments.\(^10\) However, in this and other studies, a minority of OAG patients lost field at a rate up to 1 dB per year. These rapidly progressive patients must be identified and treated more aggressively than their confreres, as they do become visually impaired more often.

A risk factor analysis was conducted to determine what attributes distinguish those becoming worse from those who were stable.\(^11\) It was pointed out that these
Practical implications of the CNTGS Study

may or may not be the same risk factors as those that determine who gets OAG in the first place. The numbers of patients were unfortunately very small for this analysis. However, women seemed at greater risk, particularly women with a subjective history of having ophthalmic or full migraine.

The conclusions of the CNTGS study were:
1. IOP lowering ‘works’; persons with lowered IOP progressed more slowly;
2. OAG is generally a slowly progressive disorder: or in the opinion of its senior authors, “Given the slow average rate of deterioration, the clinician may not need to act in haste”;
3. The target pressure concept is a reasonable approach to OAG therapy;
4. More study of risk factors for progression distinct from risk factors for incident disease is needed. Women with migraine histories may be at greater risk for progressive change.

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What have we learned from the Ocular Hypertension Treatment Study thus far?

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Introduction

Since 2002, when the primary outcome paper for the Ocular Hypertension Treatment Study (OHTS) was first published in the Archives of Ophthalmology, the ophthalmic community has been bombarded by a flurry of presentations highlighting the benefits of topical medical therapy for ocular hypertensive individuals and the importance of careful risk assessment when determining who should be treated. Although the focus has been appropriately concentrated on these issues, there is still a wealth of information generated by OHTS that warrants highlighting. Thus, the purpose of this brief overview is to highlight the key papers published to date, associated with this trial and offer take-home messages that are relevant to clinical practice.

Why was the Ocular Hypertension Treatment Study done?

There were two primary reasons for conducting such a large clinical trial involving individuals who are considered in a ‘pre-glaucoma’ stage in the disease process. First of all, there was no consensus in the ophthalmic community regarding which individuals with ocular hypertension should be treated. There were studies by several investigators who concluded that there was no protective benefit in treating patients with elevated intraocular pressures, and there were investigators who reported there was a protective benefit. Since these studies used different endpoints, employed limited treatment regimes, and included small numbers of patients, it was difficult to extrapolate the findings of these studies to clinical practice.
practice. Moreover, the evidence that treatment was in fact beneficial was questioned by economists outside the field of ophthalmology. Thus, there was a need to determine not only who should be treated, but whether or not treatment of ocular hypertension was beneficial. It was also important to perform a study that better reflected the array of therapeutic options available to clinicians, and the heterogeneity of the patient population American physicians often encountered.

What were the primary objectives of OHTS?

The primary objectives of the OHTS were two-fold: 1. To determine the efficacy of topical ocular hypotensive therapy in either delaying or preventing the transition to glaucoma, and 2. To determine the safety of topical ocular hypotensive therapy in the treatment of ocular hypertension.1

What was the study design?

Patients were randomized to one of two groups, either observation or treatment with topical medical therapy. Individuals who were randomized to medical therapy were placed on topical medication once meeting the requirements of the inclusion and exclusion criteria. The goal of therapy was an intraocular pressure (IOP) reduction to a level of 24 mmHg or lower and a 20% reduction in IOP, based on the average of the qualifying IOP and baseline IOP measurements. The final IOP goal was not necessarily 18 mmHg or lower.

There was no preset algorithm for prescribing medications. Physicians could use any of the commercially available medications. Participants underwent follow-up visits every six months; visual fields were performed at least semi-annually and stereo optic disc photography, annually. The examination of the patients semi-annually included a comprehensive history, refraction, visual acuity, slit lamp examination, direct ophthalmoscopy, and tonometry. A dilated fundus examination was performed once a year.

What were the inclusion and exclusion criteria?

Eligible patients were individuals between the ages of 40 and 80 years of age. A qualifying IOP between 24 mmHg and 32 mmHg was required in one eye, and at least an IOP of 21 mmHg and no higher than 32 mmHg in the fellow eye. Gonioscopically, angles were open and the patient had two normal, reliable visual fields as determined by the VFRC. Optic nerves were judged to be normal by the ODRC. If the patient had a visual acuity which was worse than 20/40, then the patient was excluded from the study. Patients could not have diabetic retinopathy that may interfere with the perimetric testing. If the patient had undergone an uncomplicated cataract extraction prior to entering the study, then his or her candidacy for the study could be considered.
What have we learned from the OHTS thus far?

How were the primary endpoints determined?

This is an important point, since glaucoma studies define the disease so differently, and the transition to glaucoma can often be subtle and debatable. Thus, the primary endpoint of glaucoma was defined either as a reproducible visual field abnormality or a clinically significant and reproducible change in the optic nerve. Each relevant endpoint was read by the respective Reading Center, either the Visual Field Reading Center, or the Optic Disc Reading Center. Once meeting the criteria for change, either a field defect on three consecutive fields or an optic disc change on two consecutive sets of optic disc photographs, then the patient’s medical history, visual fields, and stereoscopic optic disc photographs were reviewed by the Endpoint Committee. The Endpoint Committee then determined whether or not the changes were clinically significant and if the changes were related to primary open angle glaucoma or other causes.

Who was in the Study?

Because there was a paucity of self-reported African Americans in previous trials, a goal was set from the outset to aim to recruit sufficient African Americans, so that substantive conclusions could be made regarding this group. Thus, of the 1636 individuals enrolled in the trial, 408 patients were self-identified as African American. The baseline characteristics of the patients enrolled in the study was described by Gordon and Kass in 1999. The mean age of the participants was 55 years, more than 50% of the participants were women and 25% were African American. The baseline IOP was 24.9 ± 2.7 mmHg. There was no statistically significant difference between the baseline IOP of self-reported African Americans in the observation (25.1 ± 2.8 mmHg) and medication groups (25.1 ± 2.9 mmHg) versus others in the observation (24.9 ± 2.7 mmHg) and medication (24.9 ± 2.6 mmHg) groups. The mean horizontal cup-to-disc ratio was 0.36 ± 0.18. The cup-to-disc ratio among self-reported African Americans was higher, 0.43 ± 0.2 in the medication group, and 0.41 ± 0.2 in the observation group. Family history for glaucoma was noted in 44% of the participants. Overall, 37% of individuals had used topical medication for ocular hypertension prior to entering the study, however there were significant numbers of patients who also used systemic medications for chronic illnesses. Systemic hypertension was treated in 38%, cardiovascular disease, 6%, and diabetes mellitus, 12%. Overall, African Americans evidenced a higher proportion with hypertension, 56% versus others, 32% and diabetes, 19% versus 10%. Interestingly, heart disease was reported in only 9% of African Americans and 5% of others. Thus, a significant proportion of patients in this age group must manage systemic illnesses in addition to their ocular status.

Another interesting observation relates to the number of individuals who were not married. Since compliance with regimens for any chronic disease can be facilitated by friends and family members, the presence of interested individuals in a patient’s life can be important. A greater proportion of African Americans were either single, widowed, divorced, or separated, 52% compared to others, 30%.

Approximately two years after the last patient was enrolled in the study, central corneal thickness measurements were performed. Of the participants enrolled in
the trial, 1301 were measured. The mean central corneal thickness measurement was 573 ± 39.0 μm, generally a thicker corneal measurements compared to ‘normals.’ Almost 25% of the patients in OHTS evidenced corneal measurements which were greater than 600 μm, and on average self-reported African Americans were thinner than others.

In a subset of 439 patients enrolled in OHTS, confocal scanning laser ophthalmoscopy was performed at baseline. Of these individuals, 17% or 74 were self-reported African Americans. African Americans evidenced larger cup area, cup volume, cup depth, neuro-retinal rim area, rim volume, and smaller rim-optic disc area ratios compared to others. There was no difference when the cup shape and retinal nerve fiber layer thickness measurements were compared. Disc area appeared to account for the majority of these observed statistical differences, since the comparisons became insignificant, once disc area was considered.

Why was the protocol changed for the number of visual fields needed to confirm a defect?

Initially, patients required only one additional visual field to confirm a defect, or in other words, two fields were necessary to confirm any given defect. A field was considered abnormal if the corrected pattern standard deviation had a p < 0.05 or if the glaucoma hemifield test results were considered outside normal limits based STATPAC 2 criteria. In June of 1997, the protocol was changed in order to increase the number of required fields to three, rather than two. Since many of these technically reliable fields on retest were subsequently noted to return to normal, the ‘bar’ was raised for meeting the criteria for a confirmed field defect. Keltner and coworkers of the Visual Field Reading Center examined 21,603 follow-up visual fields. Of these fields, 1006 were follow-up retests that had been performed either due to an abnormality (n = 748) or unreliability (n = 258). A further refinement of this cohort was made, 703 or 94% of the 748 fields were abnormal and reliable, and 45 or 6% of the fields were abnormal and unreliable. Abnormalities were not confirmed for 85.9% or 604 of the 703 reliable and abnormal fields. The remarkable number of unconfirmed defects supported the change in the protocol.

How well did medications reach the prescribed goal for reduction in IOP?

The short answer is very well. The long answer is, that topical medication achieved a 22.5% ± 9.9% reduction in IOP, versus the untreated group 4.0 ± 11.6% reduction in IOP. When comparing African Americans versus others, the reduction in IOP was similar across groups: medication African Americans 22.9 ± 10.4 versus others, 22.5 ± 10.0 mmHg, and observation, 4.7 ± 13.0 versus others, 4.1 ± 11.3 mmHg. Thus, although physicians were allowed to choose their own regimen for medical therapy, the reduction in IOP not only met the goal outlined by the study, but met it very consistently.

Before leaving the topic of medical therapy, it is important to note the effect of medical therapy on the initially untreated eye. Most of the patients in this trial
What have we learned from the OHTS thus far?

were started initially on a beta-blocker (93%), however of these 761 patients, 3% did not return for a confirmation visit. Thus, the measurements of 741 patients were analyzed, and the mean time to follow-up was 32.0 ± 15.2 days. The mean reduction in IOP in the treated eye was -5.9 ± 3.4 mmHg, and in the contralateral untreated eye, -1.5 ± 3.0 mmHg. However, 45% of the contralateral eyes demonstrated an IOP reduction of 3 mmHg or more.20

Another interesting finding regarding medical therapy was, that those individuals with thicker corneas evidenced less reduction in IOP compared to those with thinner corneas. For example, among those corneal measurements ≤ 550 um, the IOP reduction was -6.8 ± 3.4 mmHg, compared to an IOP reduction of -5.8 ± 3.6 mmHg and a corneal measurement of > 590 um.21

What was the primary outcome of the Study?

The study essentially demonstrated that topical medication does indeed prevent or delay the conversion from ocular hypertension to glaucoma. After 60 months of follow-up, 4.4% in the medication group developed glaucoma, versus 9.5% in the observation group. When examining the data regarding the first POAG endpoint, 50% in the medication group and 57% in the observation group evidenced a change first in the optic nerve. This finding indicates the importance of the optic nerve in the assessment of disease status. However, it does not necessarily suggest that the optic disc is the first to change, since the level of evidence for visual field change was set so high in this study.

With regard to safety, a greater proportion of those in the medication group reported symptoms such as dryness, tearing, and itching. Of those individuals on prostaglandins 17% reported either a change in iris color, periocular pigmentation, or growth of eyelashes. However, 7.6% of the participants in the observation group also reported this finding. Other notable differences were found among systemic findings. A greater proportion of patients on medication reported psychiatric adverse events, 1.5% versus 0.5% in the observation group, and genitourinary adverse events, 5.5% among medication participants and 3.4% among those in the observation group.

A subsequent paper focused on the self-reported African Americans in the study. Of the 408 patients in this cohort who were randomized to medication, 8.4% converted to glaucoma, versus 16.1% in the observation group. The optic disc was the first to evidence POAG in 47.1% of the medication group and 48.5% of the observation group. This proportion was less when compared to others in the trial, 51.9% and 57.7% respectively.

What baseline factors ultimately proved to be important as risk factors?

The analysis of the baseline factors certainly is a very powerful aspect of this study, since it is the identification of key risk factors that can ultimately be translated into clinical practice. Gordon and coworkers22 analyzed the demographic and clinical data and determined those factors that proved to be predictive of glaucoma. Based on multivariate analyses, the authors determined that older age,
higher IOP, larger vertical or horizontal cup-to-disc ratio were predictors of glaucoma. Moreover, if a patient evidenced an abnormal pattern standard deviation on visual field testing at baseline, that individual was more likely to convert to glaucoma. Interestingly, thin corneal measurement proved to be an unexpected risk factor.

Once there was sufficient follow-up of the African Americans in the study to determine efficacy, their baseline factors were analyzed. When adjustments were made for large cup-to-disc ratio, thin corneal measurement, age, sex, history of diabetes, systemic hypertension, heart disease, IOP, and pattern standard deviation, ‘race’ was not noted to be significant as a risk factor.

Why were the rates of conversion higher for African Americans in both the medication group versus the observation group compared to others?

Since both a thin corneal measurement and a large cup-to-disc ratio were significant risk factors, the combination of these characteristics contributed to the higher conversion rate in this subgroup. This finding is important, since specific measurable risk factors can be identified, rather than the phenotypic features of a given patient.

So what are the take home messages from OHTS?

Table 1 summarizes the salient points outlined in this article. However, it is important to focus on the broader messages: 1. Topical medical therapy delays or pre-

Table 1. Notable clinical points from OHTS

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<th>Notable Clinical Points from OHTS</th>
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<td>Topical medication prevents or delays the onset of glaucoma.</td>
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<td>Topical therapy is safe for the treatment of ocular hypertension.</td>
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<td>Key clinically relevant risk factors include age, IOP, large cup-to-disc ratio, thin corneal measurement.</td>
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<td>Convergence of two key risk factors i.e. thin corneal measurement and large cup-to-disc ratio translates into a higher risk for developing glaucoma.</td>
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<td>The optic nerve is important in the assessment of patients with ocular hypertension.</td>
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<td>Differences in topographic parameters between ethnic groups such as linear cup-to-disc ratio can be explained by disc area.</td>
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What have we learned from the OHTS thus far?

vents the conversion from ocular hypertension; 2. There are no significant safety issues related to medical therapy; 3. Key clinically useful risk factors to consider include age, cup-to-disc ratio, intraocular pressure, and thin corneal measurement. Although family history did not rise to the level of significance in the analyses, clinically this factor must be considered since there is a greater likelihood that first degree siblings may develop glaucoma. Moreover, it is important to emphasize that not everyone with ocular hypertension should be treated. Other factors such as general medical status, age, and compliance with appointments must also be considered.

References

Round Table

Critiquing the clinical trials

Moderator: Eve Higginbotham, MD
Panel: Chris Johnson, MD
Peng Tee Khaw, MD, PhD
Paul Palmberg, MD, PhD
Harry Quigley, MD
Kuldev Singh, MD

Dr Higginbotham: Dr Singh, are the differences in the study designs evaluating optic nerve changes across AGIS, CIGTS, EMGT and OHTS, coloring our view of what might be the true progressive rate of glaucoma?

Dr Singh: I think a clear contrast would be between OHTS and EMGT. In OHTS, if you look at the patients that progressed based on optic nerve or field criteria, about half the patients had progressed on one or the other (endpoint reached with 55% optic nerve versus 35% visual field, and 10% combined). Whereas, in EMGT over 86% progressed and reached an endpoint by visual fields alone and 1% using optic nerve criteria. The EMGT didn’t use stereo fundus photos to examine the optic nerve. So, the old adage, if you have a hammer the whole world looks like a nail. The Swedes know and do perimetry. I think that did impact the EMGT study to a significant extent. I don’t think it overall changed what they would have found, but it perhaps did impact what the rates of progression were.

Dr Higginbotham: Harry, would you modify your rate estimate of 4% per year? What do you think about all this as it relates to the absence of consistent optic nerve evaluation techniques across trials?

Dr Quigley: I think it is a strength that the studies differed from each other, because if they had all used exactly the same method they might have all made exactly the same mistake. When you have six different studies using six different methods and the average of those results comes out to be the average I showed you, I think you have a much more; somebody used the word ‘robust’, estimate of exactly what glaucoma is doing. In truth, these studies don’t differ by very much. The progression rate in EMGT which didn’t use discs, far from being lower was higher, because they had a highly sensitive method of measuring field change. I don’t think it necessarily means glaucomatous progression is going to be faster or slower. You
can take our clinic based, non-clinical trial progression measurement that Joanne Katz and I used in a series of 75,000 visual fields from the Wilmer Institute. We came out with a 4% per year progression rate, 4% per eye per year on treated glaucoma. That’s not a clinical trial, that’s my own patients. I think that the estimates are awfully good for what glaucoma looks like.

**Dr Palmberg:** I think it’s good that all of these studies used Humphrey field testing, either with regular threshold testing or SITA. It may be possible to take all the data from these studies and develop an algorithm for risk of progression and download it into your visual field machine. As a clinician, you could have all this data from OHTS, CIGTS and EMGT, and input baseline IOP, and variation in IOP, age and disc status. The algorithm would guide your choice of target range and risk of progression. I would love to see somebody at NIH put all this data together and come up with that kind of nomogram for patients. I think it would be helpful for clinicians, because otherwise, you look at all these studies and say, “Well, what IOP should I be trying to get for this kind of patient?” Probably you could say, very advanced patients you would like to be down under 15, mild patients you would like to have a target pressure down to about 30 percent, and that works well. If you don’t have a target pressure, as pointed out in the Swedish study, some people got very little pressure lowering, they didn’t change the strategy. You found out that every millimeter of mercury does matter in this range of IOP, and that’s what Anders Heijl wanted to find out. I said, “Gee, why didn’t you have a target pressure?” He said, “Because, two things, I didn’t believe that pressure mattered under 30 very much, but if it did I wanted a pretty good measure of how much it mattered.” The EMGT study is the only study that has provided that information to us very well. The other studies, CIGTS for example, utilize a tight target range so that little progression occurs and it is difficult to detect the relationship between pressure and damage. Harry, you are right. Because these studies differ in design, you get a lot of different information. But because they share a common visual field technique, this data can be analysed across study designs.

**Dr Higginbotham:** In the early manifest glaucoma trial (EMGT), they used laser trabeculoplasty as an adjunctive treatment to medication. What do you think, Dr Khaw, about the use of trabeculoplasty as an early means of reducing pressure?

**Dr Khaw:** I have to say in Europe, particularly in British practice, the use of laser trabeculoplasty is probably completely different to its use in the U.S. Very few patients get laser trabeculoplasty. Patients will go onto medical therapy and if that doesn’t work then they will have surgery. Laser trabeculoplasty does not feature much in the British pattern of practice.

**Dr Quigley:** Laser trabeculoplasty does not figure in the U.S. base of practice either. The insurance database that we just looked at shows that of 3,500 newly diagnosed glaucoma patients around the United States, less than one percent of them got ALT within two years of diagnosis. Laser trabeculoplasty is not used very much as initial therapy in the United States. On the other hand, there are a lot of them done in the U.S., and I think trabeculoplasty is used as a standard following medicine. When you sit down and look at risk benefit ratios, laser trabeculoplasty is a wonderful therapy. We should be thinking about using laser trabeculoplasty more. We offer
it to patients as initial treatment in my practice. Most patients look at us and say, "Well, you’re saying to me it would work two out of three times, but about half of that two of three, I still have to take eyedrops anyway, right?" And the answer is right. The patient then says, "Well, I’ll start with drops then," because any rational person would probably do that. I think that’s why we don’t use ALT as the initial therapy, because the glaucoma laser trial and others show that you often don’t get there with laser alone. We need a laser therapy that is not quite so destructive and that works better.

**Dr Higginbotham:** That is going to be the question of the usefulness of selective laser trabeculoplasty. Are there any comments from the panel concerning selective laser trabeculoplasty?

**Dr Palmberg:** Yes, I think we are doing quite a bit in Miami. I don’t think we believe it works better than ALT, but there is some evidence that it causes less structural destruction, and there is the myth or the hope that it would be repeatable. SLT wouldn’t be a card you played once and then it was gone. We will need ten years to know whether that’s true. It’s not painful and it doesn’t seem to cause much in the way of pressure spikes, and sometimes it produces remarkable pressure lowering. While only one third of the people may get off medicine – I had somebody go from 37 to 17 following SLT and it seems to be holding there – for that person no medicine. It’s pretty nice.

**Dr Quigley:** Eve, a comment, but this is an area where you have two kinds of truth in the world. There is scientific truth and there is marketing truth. Someone has generated marketing truth with respect to the SLT laser that it is less damaging and it is repeatable. Until somebody actually shows that scientifically, all that is marketing truth. As Paul just said, to do that study you have to randomize people to ALT versus SLT initial therapy, wait until they fail, and then do it again, and see which one does better. There are reproducibility studies using ALT. Van Buskirk did one and it showed that 40 percent of people with repeated ALT will get a second beneficial response if they had an initial beneficial response. That is called reproducibility and it has been done with ALT. When SLT does that or runs the real good clinical trial, then I will be very excited about using it. Bear in mind the SLT treats a much larger area of the angle because its spot size is larger than ALT. Any of you who have ever done the treatment and watched pieces of meshwork come flying out as you hit the angle know darn well that SLT is not just doing some magic mumbo jumbo in there. It is hurting tissue. I am not performing SLT yet.

**Dr Palmberg:** I have taught about sixty ophthalmologists to do laser trabeculoplasty and found out that only about one-third of them could actually focus the beam on the trabecular meshwork when they were first learning this technique. One nice thing about SLT is you don’t have to be a gonioscopy maven to put a 400 micron spot size on your trabecular meshwork.

**Dr Quigley:** It has been said that laser treatment of the angle was the best thing ever done for the training of gonioscopy, and I think it is probably true.

**Dr Singh:** The one thing no one has talked about yet related to laser trabeculoplasty
is cost. I think the SLT is at least as good. No one has said it is not as good as ALT. It may be easier to use, but it’s expensive. We can’t justify buying one of these lasers, particularly because we don’t do a lot of ALT in a tertiary setting. Most of ALT is done by general ophthalmologists before they refer the patients to a university-based practice. I have a reason for why I think people don’t do as much ALT as they perhaps would, especially in academics. I think we’re busy and it’s much easier to write the script, or even have your surgery coordinator go in and sign them up for a surgery than to take time out from a busy practice or schedule a patient in and do an ALT right in the middle of your clinic or schedule a half day to do all your ALT’s. It is just that people don’t find the time. I actually think it is underutilized. We probably should do more laser trabeculoplasties.

**Dr Higginbotham:** I would say that it is underutilized. I am a big proponent of using laser trabeculoplasty considering that compliance is an issue. It is, I would say, almost like using additional med. I do a lot of selective laser trabeculoplasty. No, I have not purchased one. On the East Coast we have a gentleman who ships it to the clinic, so you can rent it for a day and you can schedule all your lasers for that period of time. The SLT does not have the same effect on the trabecular meshwork. You don’t have that scarring effect; you don’t have that same level of energy that is applied to the trabecular meshwork. I am a proponent, at least at this moment.

**Dr Palmberg:** There is a study randomizing patients to medical therapy versus SLT at initial diagnosis of glaucoma. This is what we really need – a good long term study with a lot of subjects.

**Dr Quigley:** Well, they are duplicating the GLT study, but they have not directly compared SLT to ALT. It will compare SLT to medication, no question.

**Dr Higginbotham:** Yes, we are part of that study, comparing SLT versus meds and it is headed by Jay Katz at Wills.

Let me switch gears and talk a little bit about corneal thickness. In the Early Manifest Glaucoma Treatment study, corneal thickness didn’t really come out as a risk factor, but of course in OHTS it did. Who wants to comment on central corneal thickness, how do you use it in your practice, is it really a risk factor, was it a statistical phenomenon of OHTS, is it just a phenomenon of ocular hypertensives? How should we be using this measure?

**Dr Palmberg:** I think the OHTS study did point out a couple of things. First, based on other literature, there probably is a small adjustment that should be made on the Goldmann tonometer. This is helpful when evaluating a patient with ocular hypertension; for example, you have a white patient with a thick cornea who really doesn’t have ‘ocular hypertension’. This could get one-third of the patients out of our office because they don’t have a disease, they are not even at risk over the general population to progress. I feel that is one of the most beneficial aspects of OHTS, eliminating the diagnosis in people due to an artifact related to a thick cornea. I think it is a good idea to measure central corneal thickness on everybody to save people time, money and wasted effort.

There are some people with lower pressure glaucoma, that is, they come in with
a pressure of 16 and they have a lot of damage and you find their cornea thickness is 460 and you realize the pressure is somewhat higher than measured. There are nomograms which may or may not be useful in providing a correction for IOP given a specific central cornea thickness. Maybe it is 2 mmHg for every 40 microns.

In OHTS, central cornea thickness was a major risk factor, almost greater than intraocular pressure, for those who were going to progress and develop glaucoma. There have also been a number of papers that have come out, one from Leon Herndon, pointing out a correlation between the central corneal thickness and the amount of glaucomatous damage people have at the time of presentation. The problem is when I asked him, what is the $r^2$? That is the percentage of change in one that is explained by the other - it’s 6%. It is not really all that clinically useful until they tell you that intraocular pressure was 9% when they walked in. Central corneal thickness is a risk factor, but perhaps it is being a little overplayed. Knowing the central cornea thickness may eliminate some people from being treated who have ocular hypertension, but corneal thickness does not turn out to be a major risk factor for glaucomatous progression. We need more long term data to say for sure.

Dr Quigley: The findings from the OHTS study are based on a highly selected group of people. The group is loaded with people with thick corneas because they were recruited on the basis of ocular hypertension alone. When the population based study, EMGT, looked at glucoma patients who were representative of those with glaucoma in the population, it found no effect, on tonometry yes, but no effect on who progressed more rapidly based on whether they had a thin or a thick cornea. Bal Chauhan has data from a very large longitudinal study in Canada that shows no effect of corneal thickness on progression.

We have just begun measuring, not only corneal thickness, but the corneal bioelastic response. That is, you blow air puff tonometry at the cornea and you get a measure of how much the cornea bends. You don’t really care how thick the cornea is, you care what its bioelastic response is. We have found that the bioelastic response of the cornea of the eye is a pretty good predictor of progression; it is a better predictor than corneal thickness.

Dr Higginbotham: Should we be measuring corneal thickness more than one time, should we do it every two or three years?

Dr Singh: I think central cornea thickness is fairly stable. If a patient has cataract surgery or LASIK or something else then you can recheck it, but otherwise I do not recheck cornea thickness every time. It fluctuates a little bit. With corneal thickness you are not looking for 10 or 15 micron changes; you are looking for someone who is way off the charts for guidance. One of the problems with the studies evaluating central corneal thickness and progression of disease is that a single IOP target like 12 or 18 or 15, is different for different people. Twelve is not twelve for everybody. It may be that we are under-treating those people with thin corneas because we were falsely secure with pressures of 12 to 15, when their corrected pressures are higher. It creates a bias.

The point on ocular hypertension that I want to make is that the greatest impact of OHTS in my practice has been that I have discharged people that I have been following for 10 or 15 years. These people had central corneal thicknesses of 600 to 650 microns and pressures in the low to mid 20’s; not only are they not ocular
hypertensive, they have no problem at all. I say, “See you in five years.” These are people I was seeing every six months for ten years.

**Dr Khaw:** Central corneal thickness has been very useful, because there have been occasional patients who have thick corneas, who have always measured high pressures and these patients have been overtreated to the point of having tubes and other surgeries. Helping to recognize these patients has made corneal thickness very useful. The second point is the importance of evaluating studies and their particular patient populations, because, as you say, what applies to the patients in the OHTS study does not seem to apply to other patients who have glaucomatous progression. You have to very carefully consider the specific study population.

**Dr Higginbotham:** Dr Singh, how do you use central corneal thickness to effect your treatment goal? Suppose you have a patient with a central corneal thickness of 620 microns and a pressure of 15, is that equivalent to 12? Is that good enough in a patient with advanced glaucoma?

**Dr Singh:** What you do with that patient is you follow them; if they are getting worse you lower it further. I don’t really believe Paul’s theories on 12. I don’t think 12 is any different than any other number. In that patient I would probably leave them alone. If they are 15 with a central corneal thickness of 620, that is a pretty low pressure. For most people, I would leave them alone until they show progression at that pressure.

**Dr Higginbotham:** Do you have a comment, Harry?

**Dr Quigley:** We are working against the tyranny of 21, trying to kill the idea that 21 is an important number. Paul’s finding that low eye pressure is safer than higher pressure in the normal range is unquestioned. Everybody agrees about that. But we would all hate to reestablish a new magic number for something that you have to achieve. When you have a patient with glaucomatous optic neuropathy, a new glaucoma patient, the level of pressure tonometrically doesn’t matter. That is, you are going to set a baseline for that patient based on untreated measurements two or three times and then you are going to set a target. Kuldev will argue that it should be a target zone, not a target number. You have to be flexible about it. Sure, there is a real world out there. But I advocate that you write down the baseline number and you write down your target average somewhere in the chart. Because this target IOP is different for each patient. It has to be in the same place in the chart, inside front cover, wherever you want to have it. You are going to set a 25 or 30 percent lower target whether their baseline pressure is 17, 13, or 8. The central cornea thickness helps me is if the baseline is 8 and the cornea is very, very thin. I know the ‘real’ pressure really isn’t 8, it’s really 13 or 14, and so a target of 5 makes sense, because the 5 is really 11 or 12.

**Dr Higginbotham:** How do you set a target eye pressure? We have these studies where OHTS used 20% reduction from baseline and CIGTS 40%. Do you use an absolute number? Is it a percentage reduction? What should a clinician actually do?
Dr Singh: The target pressure should depend on the patient. The real goal is to have them seeing when they die. I am happy when patients pass away with vision when I didn’t filter them. Ron Gross likes to say, good financial planning is when your last check bounces. I think that’s the analogy you use here. There is no benefit of leaving the world with more ganglion cells than you needed with hypotony maculopathy and a pressure of 3. You basically need to look at the patient and figure out a reasonable target and then see how they are doing. It is not a science, it is an art.

Dr Higginbotham: So what is your starting point? Twenty percent? Thirty percent? Forty percent?

Dr Singh: It depends on the patient. For a patient with severely advanced disease, a young African American, it may be 40 or 50 percent. For a 90 year old lady with pretty mild disease, it will be 20 percent or even 15 percent in some of these people.

Dr Higginbotham: But we know that ethnicity doesn’t matter. If the cup disc ratio is large and the corneal thickness is thin, then...

Dr Singh: Forget the ethnicity; the 90 year old with mild disease is never going to go blind from glaucoma, so that person over their lifetime doesn’t need aggressive therapy. That’s the point. It’s a race, everything combined to give an overall risk profile of that patient, and based on that you guess what the pressure should be, and it’s always a guess.

Dr Quigley: The wimpiest target is 20% lower, the most aggressive one is 50% lower, and trying to decide whether it is going to be 20%, 30%, or 50% in my practice means the 20% is the person with relatively low risk getting worse; the 50% is somebody with huge risk factors, very bad disease, and you can judge it initially based on both the risk factors you know and those you believe in, but mainly on the visual field. If both eyes are affected significantly and severely, you are not going to use 20%. You are going to say, can I get to 40 or 50 percent safely for that patient.

Dr Higginbotham: I have a couple of questions that I think are burning. Dr Quigley, you mentioned establishing untreated baseline two or three times. None of us often get patients who are not already on meds. You can’t get records of IOP before meds. Do you take patients off meds when you have them in your office for the first time, and if you do, how long do you leave them off to measure untreated baseline?

Dr Quigley: The residents joke that I take more people off medicine than I put on medicine, and that’s perhaps true because of the nature of the practice that I am seeing people after they have already seen someone else. You don’t know what the baseline is, and very often somebody was seen once by another doctor, put on medicine and for five years nobody knows what the patient’s untreated pressure is. You have no way of knowing if that patient is actually taking the medicine. More than half the time the ‘untreated pressure’ is exactly the so-called treated pressure. Because the patient was not taking the medicine. Half the patients aren’t taking their drops. If they are a terrorized person who thinks they are going blind tomorrow, I’ll see them back within the week. It is not impractical to get somebody back two or three
times. You can tell them to come anytime of the day, you have a technician in your office who might be able to do an applanation pressure. Have the patient inform the technician that they are here for an untreated pressure, get it measured and leave. Your technician doesn’t have too much to do, and you have two or three. By the third visit untreated, you start the unilateral trial. Please do start medicines unilaterally, even though there is some argument about unilateral trials. There is value in doing that to compare to the untreated eye.

Dr Higginbotham: Harry, if you detect a change in cup to disc ratio, disc hemorrhage, and no change in the visual field in one of your patients, do you modify your therapy, or if you don’t, what are the significant changes in the optic disc that you look for?

Dr Quigley: We have a stereo disc photograph in every chart that starts their follow-up and then we are using imaging in the middle for comparison. Imagine the patient has had a change in the disc or a disc hemorrhage. I tell the patient that we have evidence that they may be worsening. I tell them we are going to increase the frequency of their visual field testing. Depending upon all their other risk factors, we probably do change therapy. That means initiate therapy, or make it more intense and lower the target pressure. We certainly have a conversation with them if they are on therapy and they have a change in the disc, if they are taking drops, as to whether they are actually cooperating. That’s another whole subject, of how do you get the patient to admit they are noncompliant.

Dr Johnson: If I could make a real quick comment, I think Harry brought up a very important point and that is one of the things that multicenter trials have gotten us into is the outlook of binary outcomes, greater than 21 mmHg, less than 21 mmHg, progression, no progression. The concept of a zone of pressure reduction is nice because it looks at a continuous function. It’s not an absolute yes or no. There is a gradation, and I think that’s an important concept to keep in mind, particularly with multicenter trials.

Dr Higginbotham: Thank you, and Dr Johnson, can data from these different studies be reanalyzed with a common method for detection and progression?

Dr Johnson: I am a firm believer in Thomas Kuhn and paradigm shifts, and I think we are ready for another paradigm shift, both with structure and with function. I think of it like a frequency of seeing curve. Paradigm shifts occur when a newly introduced concept brings about an acceleration of information, but then it saturates and the field of study digests the information and you don’t learn much more until you have a new way of looking at things, a new concept. I think that we have had that with multicenter trials, a paradigm shift. Now if we can pool data, then the whole is more than the sum of its parts. When you put together the world’s best experts looking at structure and function and new ways of analyzing this material, I think you are going to come up with a new paradigm and a better method of looking at progression and change over time for both structure and function.

Dr Quigley: Eve, everybody at this table is participating in a group Doug Anderson set up that will pool all the available data of longitudinal glaucoma studies and
Critiquing the clinical trials

make that available to anybody who wants to try out new methods of detecting progression. We are working on that very aggressively in the group.

Dr Johnson: The acronym is GPS, which means we know where we are. We are trying to figure out where we are going.

Dr Higginbotham: AGIS patients were randomized to treatment type and not IOP group classification. Are these groups equal? I believe the question is related to the post hoc analysis versus the randomization study design.

Dr Palmberg: I didn’t handle the data, I suggested doing the analysis. I understand it from talking to people who performed the data analysis, that the baseline of those four groups was pretty much the same as far as their damage level. Their pressures may have been a bit different at the beginning. I have now performed a study in Miami, very similar group of patients, and the whole group comes out looking like group A with rather low pressure. At least we showed that you could do this prospectively in one group and get a similar result.

Dr Quigley: Let’s reiterate. The stratification by race and the conclusion in the AGIS study that the black patients did better than the whites or some such thing, did not take into account the severity of glaucoma that the black persons had in the study. When they did finally take into account severity, almost all of the differences became non-significant. Bear in mind that you have to take into account if a patient has bad glaucoma, it may be much more important than what their ethnicity is.

Dr Higginbotham: Dr Johnson, do you agree with the statement that good reliability visual field scores do not necessarily imply that the visual field is valid?

Dr Johnson: Yes, I would agree because when you look at the validity of the reliability measures, which we and other laboratories have done, you find that the false positive, false negative and fixation loss indicators actually underestimate the true amount of variation in terms of false positives, false negatives, and fixation losses. One thing that I think has been very valuable with the new Humphrey field analyzer is gaze tracking. There are a number of examples in the book by Doug Anderson and Mike Patella that show examples, about 15 different examples of gaze tracking. You can see when a patient is getting sleepy, when they are having a blink problem, when they are having many other kinds of issues by looking at the eye movement behavior over the test. I think there is a lot of information that is available and it can be useful. I think it is with these outliers that gaze tracking can alert you that the patient was having a problem performing the test.
Psychophysics
Update on short wavelength automated perimetry (SWAP) and frequency doubling technology (FDT) in glaucoma and neuro-ophthalmologic disorders*

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Introduction

Perimetry and visual field testing have been used as clinical diagnostic test procedures for more than 150 years. Until recently, nearly all forms of this test procedure have incorporated detection of a small white target on a uniform background. The basic procedure has undergone a variety of improvements that include the development of quantitative procedures, automation, standardization, statistical analysis techniques, age-related normative databases, and new methods of representing test results. However, detection of a small white target on a uniform background has remained the primary method of testing, although it is known that this type of procedure is responsible for stimulating nearly all types of visual mechanisms.

Recently, a variety of new specialized perimetric test procedures have been developed and evaluated.1-8 The new tests are designed to evaluate subpopulations of particular types of visual mechanisms, and to examine populations that may be more susceptible to early pathologic insults produced by glaucoma and other ocular and neurologic disorders. In particular, there are two test procedures, Short Wavelength Automated Perimetry (SWAP) and Frequency Doubling Technology (FDT) perimetry, that have demonstrated meaningful clinical improvements over conventional perimetric test procedures for evaluation of glaucoma and neuro-ophthalmologic disorders. The purpose of this paper is to provide a summary and overview of SWAP and FDT as clinical diagnostic test procedures.

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Short Wavelength Automated Perimetry (SWAP)

Color perimetry has been a topic of interest for many years. However, the practical implementation of these techniques for routine clinical use has been a bit difficult, requiring specialized technical personnel and elaborate calibration procedures. Stiles originally developed and validated the two color increment threshold technique for psychophysically isolating and measuring individual chromatic mechanisms, among which were the short-wavelength-sensitive pathways. Early studies by King-Smith and colleagues and Kitahara and colleagues found that these procedures could be clinically useful for evaluation of various ocular disorders, although only a few locations could be examined because of the length of time required to perform such testing. Approximately 18 years ago, several laboratories were able to modify an existing automated perimeter (the Humphrey Field Analyzer I) to quickly perform Short Wavelength Automated Perimetry (SWAP) testing at many visual field locations. Through these efforts, it was found that SWAP was able to detect and monitor the sensitivity of short wavelength pathways for a variety of ocular and neurologic disorders and that this information was clinically useful. On this basis of this work, it was reported that SWAP detected visual function loss earlier than standard automated perimetry, that the size of the deficit was usually larger for SWAP than for standard automated perimetry, that visual field progression could be monitored more readily, that SWAP abnormalities were predictive of future deficits for standard automated perimetry (three to five years earlier), that SWAP deficits were more reproducible than standard automated perimetry deficits, and that SWAP deficits were providing a more sensitive measure of visual field functional status. The primary limitations for SWAP included higher variability than for standard automated perimetry, and greater influences of cataract and media opacities on SWAP sensitivity. It is unlikely that any other clinical diagnostic measure of visual function has undergone the amount of scientific investigation and scrutiny that was associated with SWAP. Optimization of the SWAP procedure was conducted through the collaborative efforts of several laboratories.

Figure 1 presents the gray scale printouts for the left eye of a patient with progressive glaucomatous visual field loss for SWAP over a six year period of time. Initially, the SWAP visual field appears to be nearly within normal limits, except for the presence of an early superior nasal step. Over the next five years, this deficit progresses to become a superior arcuate nerve fiber bundle deficit. When it was first introduced commercially, SWAP took slightly longer (about two minutes) than standard automated perimetry, which limited its use in a busy clinical setting. In view of the success of the Swedish Interactive Threshold Algorithm (SITA) for standard automated perimetry, several laboratories attempted to apply this threshold strategy to SWAP. SITA is a threshold estimation procedure based on Bayesian statistical methodology that performs efficient, accurate and reliable determinations of perimetric sensitivity threshold through forecasting procedures. Several investigators have demonstrated that SITA has slightly lower variability, dramatically reduced test time, and performance (sensitivity/specificity) that is equal to or better than traditional staircase threshold estimation procedures. Early investigations of SITA SWAP indicate that it is able to perform at a level comparable to the original SWAP procedure, but with greatly reduced testing time, an enhanced dynamic range, and slightly reduced variabil-
Fig. 1. Short Wavelength Automated Perimetry (SWAP) test results for the right eye of a patient with glaucomatous visual field loss that progresses over a period of six years.

The primary purpose for SWAP testing, and which patients are best suited to undergo SWAP evaluations? This can probably best be answered by examining the areas in which SWAP provides the most useful clinical information. Many studies have now demonstrated that SWAP is able to depict early glaucomatous functional losses earlier than standard automated perimetry, which therefore means that it can be helpful in patients with risk factors for development of glaucoma but no deficits for standard automated perimetry. Additionally, in cases
where the long term status of glaucomatous damage is in question, SWAP may be able to provide helpful information because of its greater ability to reveal progressive loss. Another instance in which SWAP can be helpful pertains to glaucoma patients in whom the relationship between structural deficits (optic nerve head and retinal nerve fiber layer defects) and functional impairments (visual field sensitivity losses) are not comparable. In some instances, SWAP deficits may be more closely associated with nerve fiber losses than the results of standard automated perimetry. Finally, there are some instances in which the results of SWAP testing provides the most salient clinical information about the status and diagnosis of visual impairment.16

Frequency Doubling Technology (FDT) perimetry

The frequency doubling effect was initially described by Kelly25 and was later adapted by Maddess and Henry26 for use as a clinical diagnostic test procedure. Basically, the frequency doubling effect occurs when a low spatial frequency (less than one cycle per degree) sinusoidal grating undergoes high temporal frequency (greater than 15 Hertz) counterphase flicker. When appropriate test conditions are employed, one observes approximately twice as many light and dark stripes in the sinusoidal grating than are physically present, i.e., the spatial frequency of the grating appears to be doubled.

The initial clinical implementation of the frequency doubling effect involves determining the threshold contrast needed to detect the frequency doubled stimulus for a group of 17 (C-20 test procedure) or 19 (N-30 test procedure) targets presented on a uniform white background. This test procedure is referred to as Frequency Doubling Technology (FDT), and its initial clinical performance was published by Johnson and Samuels.27 A review of FDT clinical testing may be found in Anderson and Johnson.1 In most instances, investigators of FDT testing have reported very positive results for evaluation of retinal, optic nerve and neurologic disorders, and several laboratories have indicated that FDT testing is able to provide relatively lower variability in damaged visual field areas and earlier detection of visual sensitivity changes in comparison to conventional visual field testing.28 Figure 2 provides an example of early detection of visual field loss with FDT for the left eye of a patient with elevated intraocular pressure and evidence of a glaucomatous optic neuropathy. Results for the 24-2 Full Threshold procedure on the Humphrey Field Analyzer (Fig. 2, left) are within normal limits, whereas FDT results (Fig. 2, right) indicate a cluster of location with reduced sensitivity in the superior arcuate nerve fiber bundle region. Additionally, FDT testing has been shown to be portable and aptly suited for rapid screening, highly sensitive, specific and reliable, robust to moderate amounts of refractive error (up to four to six diopters of blur), easy to administer, and a preferred method of testing by patients.1 Current studies also indicate that it is possible to follow patients longitudinally with FDT testing, and the findings to date are quite positive.29-31 As with all test procedures, the original FDT test procedure has several disadvantages, including limited spatial resolution and being affected by cataract and other media opacities.

Recently, a second generation FDT device, known as the Humphrey Matrix, has
Fig. 2. An example of frequency doubling technology (FDT) perimetry results (right) obtained in the left eye of a patient with a normal visual field on standard automated perimetry using the Humphrey Field Analyzer II (right), but who has evidence of a glaucomatous optic neuropathy and additional risk factors for glaucoma. Note that the FDT findings indicate a cluster of locations in the superior arcuate nerve fiber bundle region with reduced sensitivity.
Fig. 3. An example of Humphrey Matrix Frequency Doubling Technology (FDT) perimetry results using the 24-2 test presentation pattern for the right eye of a patient with normal vision (left) in comparison to findings obtained for standard automated perimetry using the Humphrey Field Analyzer II (right).

been introduced to improve the test procedure and minimize its disadvantages.\textsuperscript{32} The Humphrey Matrix performs most of the procedures that were introduced for the original FDT device, plus some additional features: (1) Smaller targets arranged in a grid pattern according to a 24-2, 30-2, 10-2 and Macula stimulus presentation pattern; (2) floppy disk and CD storage capabilities; (3) a video-based eye movement monitor; (4) the ZEST (Zippy Estimation of Sequential Thresholds)
threshold estimation strategy; (5) an improved video display panel and hard copy printout; (6) an enhanced statistical analysis package; and (7) many other features.

A thorough overview of the Humphrey matrix has been published. Multicenter trials designed to examine the Humphrey Matrix for evaluation of visual field loss in retinal disease (age-related macular degeneration and diabetic macular edema), glaucoma, other optic neuropathies, chiasmal and post-chiasmal visual field loss.
disorders indicate that the Humphrey Matrix demonstrates high sensitivity and specificity, correlates well with the results from the Humphrey Field Analyzer standard automated perimetry procedures and has a test-retest variability that is relatively constant over its entire dynamic range.

Figures 4-6 present the results of Humphrey Matrix (right) and Humphrey Field Analyzer (left) test results for the right eye of a patient with normal vision, and the
Fig. 6. An example of glaucomatous visual field progression noted for the Humphrey Matrix FDT for the left eye of a glaucoma patient with a superior arcuate nerve fiber bundle loss that was measured over three successive years.
right eye of a glaucoma patient, right eye of a patient with age-related macular degeneration (10-2 stimulus pattern), respectively. It will be noted that there are good correlations between the results of the two test procedures, although it is sometimes found that the Humphrey Matrix reveals earlier or more extensive visual field losses. The initial clinical evaluation of the Humphrey Matrix indicates that it demonstrates good performance characteristics. Figure 6 presents Humphrey Matrix results obtained for the left eye of a glaucoma patient over three successive years to demonstrate its potential ability to determine glaucomatous visual field progression.

Summary

SWAP and FDT perimetric testing have been shown to be effective clinical diagnostic test procedures that present many advantages for practitioners and patients. Many other test procedures have been developed and evaluated during this time period, but have not been able to demonstrate their importance and extent in a clinical setting when compared to SWAP and FDT. Further research should serve to enhance the clinical effectiveness of these two diagnostic test procedures.

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Update on SWAP and FDT

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Questions and Answers

Presiding Physician: Jonathan Calkwood, MD

Dr Calkwood: What does a patient with a defect on FDT see in that area of the defect? Do the patients more often appreciate it, or are you picking up subclinical defects that perhaps the patient does not notice?

Dr Johnson: The task with frequency doubling is whether or not you see the target that is being presented. It is a flickering target. There has been an issue of whether subjects see only the flicker or the flicker plus the grating pattern of light and dark stripes. For the most part, the difference in the amount of contrast necessary to detect either a flicker or to definitely detect stripes is very small. Essentially, the task for the subject is 'Can you detect a change in that portion of the visual field?' How that relates to what patients see in the world is another issue. We don't have information on that.

Dr Calkwood: Can you use Matrix to follow glaucoma, or is it a screening test?

Dr Johnson: We have six years of longitudinal follow-up with the precursor, QuadraVision to the Matrix and we have some people that have shown progression. There is a glaucoma change probability that is being developed right now at several centers. I think because of the early detection and the spatial characteristic advantages, there will be some distinct benefits for that. We need to do the longitudinal studies to get the definitive information. I am an empiricist and I go by what the data shows.

Dr Calkwood: Should clinicians to stop using SWAP and move over to Matrix?

Dr Johnson: I think it has much more capability than the first generation FDT device to monitor progression over time, but I also think we need more results. Matrix is still fairly new and we need to see what other centers do with that. I was mentioning a while back to someone that one of the things I think is a true test of how well a diagnostic instrument does is how other people use it. I always look to see what other people say, because I think that is really the true test.

Dr Johnson: A question from the floor – Is the SWAP normative database valid and has the SITA-SWAP normative database been adjusted properly? We had multiple centers involved in the SITA-SWAP determination for normals. There was a little bit of controversy about the normative database for SWAP initially and it had to do with the amount of variability in the superior visual field. There have been instances pointed out to me by Jamie Brandt where a
patient had a superior arcuate defect that was reproducible on SWAP. They had an optic neuropathy that was consistent with glaucoma, but their standard white-on-white field was normal. This was a reproducible SWAP deficit superiorly, but the normative database said it was within normal limits. That is an additional challenge that we need to do better on establishing a normal database, particularly with regards to SWAP. It is important, especially for SWAP, to tape the superior brow when a droopy lid is present. This is more important for SWAP than for standard testing. In general, it is a good normative database, but I think it can be improved and refined.
New developments in perimetry, including SITA, ZEST and TOP

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Introduction

In the past thirty years, perimetry has advanced from the use of manual procedures to automated visual field testing. This has produced a number of clinical benefits, including standardization of test results within and between clinical ophthalmic centers, quantitative evaluation and analysis of results, automatic comparison to age-adjusted normative values, enhancements of the accuracy and efficiency of tests, and many additional features. These advances have significantly improved the diagnostic utility of perimetry and visual field testing in glaucoma patients. Recently, there have been several new additions to automated perimetry that have provided further beneficial effects, consisting of new functional assessment techniques, threshold estimation procedures, and data analysis methods. This chapter will provide a brief review of the innovative advances in these three areas of perimetric research development.

New test procedures

Among the new test procedures that have been shown to be useful for evaluation of glaucomatous visual field loss are Short Wavelength Automated Perimetry (SWAP), Swedish Interactive Threshold Algorithm (SITA) SWAP, Frequency Doubling Technology (FDT) perimetry, and Humphrey Matrix FDT perimetry. Because these test procedures have been described in a previous chapter of these symposium proceedings, further discussions of them will not be provided here. However, it will be noted that these techniques have all been shown to be of great clinical value for detection and evaluation of glaucomatous visual field loss.1-10

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Rarebit perimetry is also a new technique that uses a computer monitor (LCD display) to present very small stimuli (individual dots) on a dark background. Each stimulus presentation consists of one or two dots presented in a predetermined pattern that is part of a larger cluster of points. Details of the rarebit perimetry technique can be found in several current references. The arrangement of dots is designed to detect early visual field losses in glaucoma and other ocular and neurologic diseases. The patient’s task is to indicate for each presentation whether one or two dots was observed. The stimulus-response relationships are then used to evaluate the visual field status at each location, and an indication of normal, partially abnormal or complete abnormal visual field performance is noted. To date, the results that have been published for rarebit perimetry are encouraging from a clinical perspective.

Multifocal visual evoked potential (mfVEP) assessment is another new procedure for evaluating visual field sensitivity. mfVEP obtains electrical signals from electrodes placed over the occipital cortical region in response to an alternating checkerboard pattern. The stimulus consists of 60 sectors, each of which uses a 16-element alternating checkerboard pattern, located throughout the central visual field. The size of the checks and the 16-element pattern are scaled to approximately compensate for the amount of visual field incorporated by individual checkerboard patterns. A modified binary m-sequence, a temporal delay for the m-sequence corresponding to each segment, and sophisticated cross-correlational mathematical analyses are used to extract the local visual field components of the VEP signal. The duration of testing is approximately 10-15 minutes to obtain data for each eye or both eyes together.

Figure 1 presents the Humphrey Field Analyzer II (HFA II) standard automated perimetry gray scale representations of the visual field for the right and left eyes (top) in comparison to the mfVEP results (bottom). The HFA II findings indicate that the visual field of the left eye is within normal limits, but the right eye has an inferior arcuate nerve fiber bundle defect. The mfVEP outputs for the left and right eyes are presented together, with the responses from the left eye indicated by red traces and the responses from the right eye represented by blue traces. Note that for the superior visual field, both eyes provide similar and consistent VEP waveforms at nearly all locations, whereas the left eye results appear normal for the inferior visual field, but many of the right eye traces in the inferior visual field are flat, indicating sensitivity loss. There is very good correspondence between the mfVEP and standard visual field properties.

The mfVEP visual field assessment procedure is clinically useful because it is possible to obtain visual field information from the mfVEP for patients who may be unreliable, fatigue easily or who are not able to perform standard automated perimetry. It also is able to provide confirmatory findings to substantiate other associated clinical findings. Finally, there are also some preliminary findings that suggest that this procedure may find early losses that are not observable with standard automated perimetry until some time later.
New developments in perimetry, including SITA, ZEST and TOP

New test strategies

Three new threshold estimation test strategies have been developed for use in automated perimetry: (1) the Swedish Interactive Threshold Algorithm (SITA); (2) Zippy Estimation of Sequential Thresholds (ZEST); and (3) Tendency Oriented Perimetry (TOP). The intent of these data acquisition procedures is to maintain or improve the reliability and reproducibility of the procedures while reducing the testing time. Two of the procedures (SITA and ZEST) are based on Bayesian statistical principles, while the third procedure (TOP) is a spatial averaging test procedure.

Fig. 1. Humphrey Field Analyzer II gray scale printouts (top) for the left and right eyes of a patient with glaucomatous visual field loss in the right eye, consisting of an inferior arcuate nerve fiber bundle defect. Multifocal visual evoked potential (mfVEP) waveforms at individual visual field locations for the left (red) and right (blue) eyes of the same patient (bottom). Note that there is good correspondence between the absence of a recordable mfVEP waveform and reduced sensitivity at similar damaged visual field locations in the right eye.
Swedish Interactive Threshold Algorithm (SITA)

SITA is a forecasting-based test strategy that utilizes Bayesian statistical principles. A detailed description of the SITA test procedure is beyond the scope of this paper, so a brief overview of SITA will be presented. The basic rationale underlying the SITA test strategy is to combine information that is known about the visual fields of normal and glaucomatous eyes (e.g., prior probabilities), the responses of the patient during the test procedure, and the interrelationship among neighboring visual field locations to make accurate, efficient and reliable estimates of visual field sensitivity by using forecasting methods. For both normal and glaucomatous eyes, SITA incorporates a probability density function (pdf) for each visual field location, which represents the frequency distribution of possible sensitivity values for individuals of different ages. The mode of this distribution is then employed to provide a best estimate of sensitivity for each visual field location prior to testing. A test stimulus is presented and, depending on the patient’s response (‘seen’ or ‘not seen’) and their frequency of seeing curve (‘likelihood function’), the next stimulus presentation is then determined (‘maximum likelihood function’). This process continues for each visual field location until the 95% confidence limits are within a predetermined range (dynamic termination criterion), at which point a sensitivity estimate is generated. The SITA Standard test procedure has a more stringent dynamic termination criterion (smaller 95% confidence range) than the SITA Fast procedure. As expected, the SITA Fast procedure is more efficient, but also has greater variability and is more susceptible to response errors and inconsistencies. Throughout the test procedure, the pdf models for normal and glaucomatous eyes are assessed to determine which best corresponds to the patient’s response behavior for each visual field test location. When all visual field locations have been tested, SITA compares the sensitivity of each visual field test location with its immediate neighbors to ascertain which locations need to be retested and to perform a mathematical adjustment of final sensitivity estimates.

A number of studies have now confirmed that SITA Standard sensitivity estimates correlate highly with those obtained using the full threshold staircase procedure (although the average SITA sensitivity estimates are approximately 1.2 dB higher), have lower within- and between-subjects variability, dramatically reduced testing time, and improved sensitivity for detecting and evaluating visual field loss. As indicated previously, the performance of the SITA Fast strategy indicates an improvement in efficiency, but at the expense of degraded accuracy and precision. A large number of clinical practitioners use the SITA test strategies as their standard test procedure, which attests to its clinical value.

Zippy Estimation of Sequential Thresholds (ZEST)

The ZEST sensitivity estimation procedure is quite similar to the SITA procedures, and is based on Bayesian statistical principles. However, there are some important differences between ZEST and SITA. First of all, SITA uses two pdf (normal and glaucoma) for each visual field location, whereas ZEST uses a single clinical pdf, consisting of a mathematical combination of the normal and glaucoma pdfs.
New developments in perimetry, including SITA, ZEST and TOP

In some instances, the starting pdf for ZEST is a flat pedestal, which indicates that prior to testing, all possible sensitivity values are equally likely for each visual field test location.\(^{22}\) This simplifies the test procedures and minimizes the number of assumptions made prior to testing. Secondly, ZEST uses the mean of the pdf to determine its estimated sensitivity prior to each presentation, whereas SITA uses the mode of the pdf. Earlier research has demonstrated that the use of the mean improves the accuracy, precision, efficiency and robustness of this type of test algorithm.\(^{19-21}\) Thirdly, ZEST uses a fixed number of presentations as a criterion to stop further testing, as compared to the dynamic termination criterion employed by SITA.\(^{22}\)

What are the ramifications of these changes produced by ZEST in comparison to SITA? First of all, ZEST has greater consistency in the duration of testing as compared to SITA. For example, a test that normally takes approximately five minutes per eye to complete with ZEST will vary by a range of approximately ± 20 seconds irrespective of glaucomatous visual field damage,\(^{22}\) while there can be a considerable variation in testing time (within and between subjects) for SITA, depending on the status of the visual field.\(^{17}\) Secondly, the variability of ZEST remains relatively constant throughout the entire dynamic range of testing,\(^{23}\) while the variability for SITA increases in moderately damaged visual field locations.\(^{17}\) Finally, current reports indicate that the clinical accuracy and precision of ZEST is highly comparable to that of the SITA and Full Threshold test algorithms, despite its distinct advantages for efficiency and consistency.\(^{21}\)

**Tendency Oriented Perimetry (TOP)**

TOP is a spatial averaging procedure that combines information from neighboring visual field test locations to estimate sensitivity.\(^{24-26}\) The basic test strategy employed by TOP is a staircase reversal procedure similar to the Full Threshold technique. Rather than applying the staircase procedure to individual visual field locations, however, TOP analyzes groups of neighboring visual field locations, as illustrated in Figure 2. Beginning at visual field locations marked by a 1 in Figure 2, stimuli are presented. Depending on whether the stimulus was seen or not seen, new stimuli are presented at the locations marked 2. This process continues for locations 3, 4 and second presentations for locations 1-4 until a satisfactory estimate is obtained.

TOP is a simple test algorithm that demonstrates reasonably good clinical performance, correlates well with other test procedures and is highly efficient.\(^{24-26}\) In this view, it represents a valued clinical tool for visual field evaluation. However, TOP also has some deficiencies. Because it is a spatial averaging procedure, TOP will underestimate or completely miss small or shallow visual field deficits.\(^{26}\) Similarly, it will underestimate the slope of more extensive visual field defects at their boundaries.\(^{26}\) This limits the ability of TOP to detect small, shallow defects and monitor the progression of larger defects, which can adversely impact the ability to properly monitor patients.

To summarize, recent advances in perimetric test strategies have improved the efficiency, accuracy, reliability and precision of estimating sensitivity. Further improvements will help to advance these techniques for the future.
A number of methods have been developed to evaluate progressive glaucomatous visual field changes over time. Unfortunately, the techniques that are used to determine visual field progression are quite different from one multicenter clinical trial to another, there is only partial agreement among the various techniques, and no consensus among investigators can be achieved at this time. Direct comparison studies of the various methods to determine visual field progression have been obtained from several laboratories to corroborate these conclusions. Although there is still controversy and lack of consensus among investigators, there are several results that elicit good agreement for achieving high sensitivity and specificity: (1) careful procedures and quality control assessment methods are necessary; (2) groups or clusters of locations provide better sensitivity/variability trade-offs than an analysis of individual locations or global visual field summary statistics; and (3) confirmation of suspected visual field changes are necessary through repeated testing.

One method that was developed in conjunction with the Early Manifest Glaucoma Trial (EMGT) and is available commercially for the Humphrey Field Analyzer II is the Glaucoma Progression Analysis (GPA) procedure. Based on extensive visual field data, the GPA procedure will evaluate either Full Threshold data, SITA results, or a combination of test procedures. The GPA analysis procedure averages the first two visual fields (either Full Threshold or SITA) to establish a baseline, and then compares subsequent visual field results to the baseline char-

Fig. 2. Illustration of the pattern of responses obtained at neighboring visual field locations that are part of the Tendency Oriented Perimetry (TOP) test strategy.
Fig. 3. An example of baseline (left graph) and follow up (center and right graphs) Humphrey Field Analyzer II visual fields obtained over a six year time period for the left eye of a patient with glaucoma. The Glaucoma Progression Analysis (GPA) evaluation procedure was employed to assess the results. Note that there is progressive visual field loss in this case, and printed indications of 'possible' (three or more locations that are outside normal limits on two successive visits) and 'likely' (three or more locations that are outside normal limits on three successive visits) progression.
characteristics to determine whether the results are stable or whether improvement or progression has occurred for each test location (using different symbols to denote improvement and progression). The determination of change (improvement or progression) is based on the variability characteristics obtained in a group of glaucoma patients who were tested four times over a one month time period. The difference between baseline and followup results is determined for each test location, based on its visual field position and current sensitivity. If the difference is within the 95% confidence limits, then no change is indicated. A value that is

Fig. 4. Printed output of the most recent visual field findings for the Humphrey Field Analyzer results for the same patient’s eye shown in Figure 3, along with a ‘snapshot’ overview of the GPA results obtained to date.
outside of the 95% confidence limits is denoted as progression (worsening) or improvement (better sensitivity). The procedure also checks to determine whether this suspected change at a specific location is confirmed on subsequent visual field examinations. If three or more test locations with significant worsening change are confirmed on two successive visual field examinations, the result is called ‘possible progression’, and if three or more abnormal locations are confirmed on three successive visual field examinations, the results is called ‘likely progression’. In this manner, a consistent criterion can be applied to follow up visual field data to evaluate visual field progression in a fashion that will maintain high sensitivity and specificity.

Figure 3 presents an example of visual field progression, consisting of two baseline visual fields and four follow-up visual fields obtained over a six year time period. The first two follow-up visual fields show changes that have occurred since the baseline visual fields, and ‘possible progression’ is indicated. After 3 and 4 follow-up visual fields, the affected regions are again confirmed, so a designation of ‘likely progression’ is presented.

In many instances in the clinic, it is difficult to peruse all of the visual field data that has been obtained for a particular patient, and maintaining all of the individual visual field printouts in the chart can be difficult. For this reason, a shortcut procedure is also available, which presents the current visual field results and a box summarizing the GPA results, as shown in Figure 4. This provides a rapid means of presenting the most salient visual field data for clinical purposes.

Recent advances, in new perimetric test procedures, accurate and efficient testing strategies, and sophisticated analysis procedures have enhanced the clinical utility of perimetry and visual field testing for monitoring glaucoma. Future advances in these areas will serve to improve the diagnostic capabilities of these procedures even further.

References


Evaluation of visual field loss in glaucoma: Progression and classification of perimetric damage*

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Introduction

The ability to accurately and reliably determine whether a glaucoma patient’s visual field is stabilized or is undergoing progressive loss is a vital aspect in their clinical management. The efficacy of treatment is usually based on this evaluation, in conjunction with other related clinical information, including the status of the optic nerve head and retinal nerve fiber layer. In some instances, changes in the appearance of the optic nerve head and alterations in the visual field reveal similar characteristics, as illustrated in Figures 1 and 2. Figure 1 presents a composite of optic nerve head photographs of the left eye of a glaucoma patient, that were obtained at our visual function testing center over six successive years. For illustration purposes, the optic disc photos are presented as monocular images, but each photo represents one half of a stereo pair. It can be observed that there is inferior neuroretinal rim thinning, inferior retinal vessel displacement and other features that indicate that there has been structural progression of glaucomatous damage. Figure 2 presents the 30-2 and 24-2 visual fields of the left eye for the six successive years, using the Full Threshold and SITA-Standard threshold test strategies. It can be observed that there is a superior visual field loss (nasal step) that develops and the progresses to become a superior arcuate scotoma. In this example, there is a reasonably good correlation between the structural damage to the optic nerve head and the functional visual field loss. However, there are also many instances in which the optic disc reveals progressive glaucomatous damage that is not evident for the visual fields, examples in which the optic disc appears stable but the visual field shows evidence of progressive loss, and other cases in which the damage revealed by the optic disc and visual field do not correlate well.

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Another factor that makes it difficult to assess glaucomatous visual field progression is variability. As summarized in Spry and Johnson, a considerable amount of within session (during a visual field examination) and between session (successive visual field examinations) variability can occur, particularly in damaged visual field locations where variability can be three to four times higher than for normal locations, and 95% confidence limits can span nearly the entire effective range of the instrument. This dilemma is nicely depicted in Figures 3 through 7, which present visual field results for the same left eye obtained in a glaucoma patient at six-month intervals over a 7.5 year time frame (15 visual fields). Over the first three visual fields (Figure 3) the patient appears to get worse, but then improves over the next three visual fields (Figure 4). The patient then gets worse over the next three visual fields (Figure 5), gets better over the next three visual fields (Figure 6), and then gets both better and worse for the final three visual fields (Figure 7). How does one reasonably decide whether this eye got better, worse or stayed the same? One could make a convincing case for each of these options by selecting the proper sequence of two or three successive visual fields from the entire array.

Fig. 1. Optic disc photographs of the left eye of a glaucoma patient over six successive years of evaluation (1998 through 2003). There is thinning of the neuroretinal rim and displacement of blood vessels inferiorly, indicating progressive glaucomatos damage to the optic nerve.
Each of the major multicenter trials in glaucoma has found that it is necessary to confirm suspected visual field and optic disc changes in order to maintain high specificity (correctly identify stable results by adopting more stringent criteria). A good example of this has been reported for the Ocular Hypertension Treatment Study (OHTS), where it was shown that more than 85% of all new, suspected visual field changes or abnormalities were not confirmed on the next subsequent visual field examination. Nicolela and colleagues have also classified glaucomatous disc damage into four categories: focal, myopic, senile sclerotic and generalized deficits. Their longitudinal findings indicate that patients with senile sclerotic optic discs are less likely to undergo glaucomatous visual field or optic disc progression.

Fig. 2. Six years of successive visual fields obtained in the left eye of the glaucoma patient whose optic disc photographs are shown in Figure 1. There is the development of a superior nasal step, which progresses over time to produce a superior arcuate nerve fiber bundle defect, correlating well with the optic nerve head damage.
Fig. 3. Three sequential visual fields (December 1984 to July 1986) for the left eye of a glaucoma patient. Over this time period, the visual field appears to get worse.

Determination of glaucomatous visual field progression has continued to be an enigma for clinical investigators, and this has been distinctly pointed out by the fact that each of the multicenter clinical trials in glaucoma use a different criterion for distinguishing between stable and progressively changing visual fields. The Advanced Glaucoma Intervention Study (AGIS) divides the central visual field into a number of localized regions, and assigns a value to each zone based on the summed visual field sensitivities for each area. A composite added score between 0 (normal visual field) and 20 (end stage glaucomatous visual field loss) is derived from this calculation. Progression is defined as an increase in visual field score by four or more from baseline fields, and confirmed on two successive visual fields.
Fig. 4. Three additional sequential visual fields (January 1987 to October 1987) for the left eye of the glaucoma patient shown in Figure 3. Over this time period, the visual field appears to get better.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) uses a similar pattern as AGIS, but bases the scoring on Total Deviation probability values rather than sensitivity values. The scoring system again is between 0 and 20, and progression is defined as an increase in visual field score by three or more from baseline fields, and confirmed on two successive visual fields. The Early Manifest Glaucoma Treatment (EMGT) considers visual field progression to be three or more visual field locations that become significantly worse (p < .05) than baseline on the Glaucoma Change Probability (GCP) analysis and are confirmed on two successive visual fields. GCP in this case is based on Pattern Deviation values rather than Total Deviation values in order to minimize the influence of cataract and other...
Fig. 5. Three additional sequential visual fields (August 1989 to October 1990) for the left eye of the glaucoma patient shown in Figures 3 and 4. Over this time period, the visual field appears to get worse.

media opacities on GCP results. The currently available Glaucoma Progression Analysis (GPA) procedure was based on this information and it also takes into account the evaluation of data obtained using the SITA test strategy. The Primary Treatment Trial (PTT) uses pointwise linear regression of individual visual field locations for successive visual field examinations, and defines progression as two or more locations with regression slopes that are statistically significantly different from zero (p < 0.05). The Normal Tension Glaucoma Study (NTGS) used kinetic testing on the Goldmann perimeter, and defined glaucomatous visual field pro-
Fig. 6. Three additional sequential visual fields (March 1990 to January 1991) for the left eye of the glaucoma patient shown in Figures 3-5. Over this time period, the visual field appears to get better.
Fig. 7. Three additional sequential visual fields (July 1991 to March 1992) for the left eye of the glaucoma patient shown in Figures 3-6. Over this time period, the visual field appears to get worse and then better.

sion, and it is both interesting and important to determine how they compare with each other. Several studies have reported that when these criteria are used to evaluate the same data set, there are dramatic differences in the sensitivity and specificity of the procedures, and that there is only 50-65% agreement among the various methods. As a consequence, glaucomatous visual field progression remains an unresolved question, and no consensus has emerged among investigators regarding which method (or new methods) are the most appropriate ones to use.

The current procedures for evaluating glaucomatous visual field progression may be divided into four basic categories, and multicenter trials employing these
techniques are indicated in parentheses: (1) Clinical judgment of visual field progression (NTGS). The advantage of this procedure is that it is the one most commonly used on a routine clinical basis. The disadvantages include large variation among evaluators and non-quantitative methods of analysis. (2) The use of classification methods (AGIS, CIGTS) of determining visual field progression. The advantages of this method are that it is quantitative and standardized. The disadvantages are that the decision rules are only partially based on prior data, and the nature of the 0-20 numeric scale (e.g., linear versus non-linear) is not known. (3) Event analysis (EMGT) of glaucomatous visual field progression. The advantages of this procedure are that it is based on prior data, is quantitative and accounts for variability. The disadvantage is that it only compares the current visual field to baseline values, primarily ignoring the interim visual fields. (4) Trend analysis (linear regression) of glaucomatous visual field progression. This approach has the advantages of standardization and quantification. The primary disadvantage of this approach is that seven to eight visual fields are necessary to achieve high sensitivity and specificity.

Glaucomatous visual field progression can occur in many forms. Scotomas, or areas of visual field loss can become deeper, can become larger or can develop in new areas. There is clearly a need to develop and refine existing methods of evaluating visual field progression in order to achieve consensus among investigators. In the interim, what can be done to provide the best and most clinically useful procedures for determining progression? Additional research will be needed to properly answer this question.

Classification of visual field loss in glaucoma is performed to evaluate the frequency, location and shape of perimetric deficits. 8-10 This can be of great clinical use in determining the earliest visual field deficits from glaucoma, whether or not the visual field loss is consistent with glaucomatous damage or is more likely to be due to other ocular or neurologic disorders (differential diagnosis) and whether sequential visual field deficits appear to be stable or are undergoing progression. A number of investigators have evaluated various classifications for glaucomatous and other visual field deficits, and brief overviews have been published.8-10 In many instances, these classification systems have been based on cross-sectional results from a group of patients. Fortunately, the Ocular Hypertension Treatment Study (OHTS) permitted initial glaucomatous visual field loss to be monitored on a longitudinal basis, and therefore served as an excellent source for developing a glaucoma visual field classification system. The purpose of this endeavor was to develop a visual field classification system that would permit glaucomatous visual field deficits to be readily detected, distinguished from visual field loss due to other ocular or neurologic dysfunction, and was reproducible and accurate among different visual field readers.

We performed an evaluation and refinement of a visual field classification system for OHTS. 8 The final classification system consisted of 17 mutually exclusive patterns of visual field loss that was able to distinguish among artifactual test results (droopy eyelids, trial lens rim artifacts, etc.), glaucomatous visual field losses (nasal steps, arcuate defects, etc.) and non-glaucomatous visual field deficits (hemianopic defects, centrocecal scotomas, etc.). A detailed description of the criteria used to perform the visual field classifications is included in the original publication. 8

Over 38,000 visual fields of 1,636 participants in the OHTS investigation (greater
than eight years of follow up, with visual fields performed every six months, plus visual field retests when necessary) were evaluated by three visual field readers. The results of this evaluation were quite positive. There was agreement by two out of three readers 97% of the time, and agreement by all three readers approximately 2/3 of the time. Reproducible evaluations (test-retest) were obtained by all three readers approximately 88.5% of the time. The severity of visual field loss associated with each of the 17 classifications was also determined, along with the prevalence of various visual field deficits. Nearly 60% of the visual field deficits were felt to be consistent with glaucoma. These results indicate that a classification system for visual field loss in glaucoma can be successfully achieved.

Evaluation of visual field information can be a complex and difficult procedure, although a careful and informed approach to visual field analysis can be of tremendous clinical value. This publication illustrates some of the problems encountered when assessing visual fields, but also provides some helpful guidelines for the practitioner interested in obtaining the maximum benefit from these methods. In the future, there are at least two issues that can be addressed to improve our ability to determine visual field progression and characterize deficits. First, performance can be enhanced by methods that are able to reduce variability, either through the development of new test procedures or through improved analysis techniques. Secondly, methods that are able to indicate larger and more sensitive changes, either through test procedures or analysis techniques, could significantly improve the ability to determine visual field properties and classify losses in ocular disorders. Further research will be necessary to elucidate and evaluate these new approaches.

Many practitioners will indicate that these future goals are desirable, but they are also highly concerned about what can be accomplished at the present time. The primary current objectives are to utilize all of the information that is currently available, including the visual field analysis procedures that are currently available, application of the best available test strategies and procedures, the use of careful quality control methods for performing the test, confirmation of suspected changes, the implementation of appropriate decision rules and interpretation guidelines, and consideration of all available clinical information and patient medical history when evaluating visual field information. Together, these procedures can provide the clinical practitioner with an accurate and informed basis for evaluating visual field information.

References

Round Table

Detecting and monitoring progression

Moderator: Harry A. Quigley, MD
Panel: Chris Johnson, MD
Andrew G. Lee, MD
Eve Higginbotham, MD

Dr Quigley: I am going to stick to questions that would be highly relevant to what you are going to deal with next Monday morning when you sit down to see the next glaucoma patient, because probably thirty to forty percent of the patients you see in a general ophthalmology clinic have a glaucoma related problem. One of the things you might need to talk to your glaucoma patients about is what is the likelihood that they are going to go blind. Or to put it in a more useful way, what is the likelihood that the average glaucoma patient is going to get worse in a given year in one eye? Dr Johnson, have you ever given thought to that question? Just as a proportion for example, what do you think is the chance that the average glaucoma patient under standard treatment being given by these fine doctors out here in the United States is going to have a worsening of visual field in one eye or the other one in a given year of follow-up? Is it a high chance? Is it a low chance? The world’s literature does have some answers, and I will be happy to provide that later. Dr Johnson, what do you think the chances are?

Dr Johnson: I wrote an editorial for the Journal of Glaucoma a few years ago about something that was a paradox to me, and that is when you go into a glaucoma clinic there are all these people with optic disc abnormalities and with visual field loss, but to me one of the things that has been interesting is doing longitudinal studies. You study hundreds of patients for five, ten, fifteen years, and only a small proportion of them change and develop glaucoma if they are at risk. That has happened with the ocular hypertension treatment study.

Dr Quigley: This is very important. This is moving from glaucoma suspect status to having a visual field defect. In a few moments we are going to ask, what is a visual field defect? Before this is done we will define what a visual field defect is.

Dr Johnson: But my general conclusion was the best thing you can do for someone who is at risk of developing glaucoma or who may be progressing if they have glaucoma, is to enroll them in a multicenter clinical trial, because most of them don’t change.
Dr Quigley: Why do you think Chris Johnson’s opinion is that clinical trials would have a beneficial effect on the view of what glaucoma progresses like? Would persons in clinical trials be just like the people in your office? Why are they different? Why are the people who volunteer for clinical trials different from the average patient in the community?

Dr Khaw: They are selected.

Dr Quigley: What are their characteristics? They are dumb enough to sign up for an experiment. Why would they do that? Because they trust the heck out of these doctors up here. And they show up for their visits. If they don’t, you go after them, you bring them back in. So they have 100% cooperation with visits. For many studies – the drugs are free. The Ocular Hypertension Treatment Study – how many people paid for their eyedrops? You eliminated the cost problem of cooperation. I am going to use those clinical trials data anyway.

Eve, what would you say? How many glaucoma patients get worse in a given year? You have a person who has visual field damage of a type we are going to detail in a few moments because we are going to say what a field defect is. But imagine we know so far what a field defect is. The person is under medical therapy for their glaucoma with a 0.8 cup in each eye and a Humphrey visual field defect, and you are treating them with some nice combination of eye drops. What is the chance that that patient is going to get worse in a given year? Is it five percent? Is it twenty percent? Or is it fifty percent?

Dr Higginbotham: Pretty low.

Dr Khaw: Pretty low. We audited figures recently and it is definitely less than five percent.

Dr Quigley: What I would take as the take-home message from that is that if you think a patient of yours is progressing, they probably aren’t. I teach that to the residents over and over and over again. Because what that leads to in my opinion is that you don’t get in trouble as much. You are much more likely to be right if you guess the patient is not progressing than if the patient is progressing. There are some other corollaries to that. What do you do to prove that the patient is or isn’t progressing? Dr. Johnson, what did you do in your clinical trials? Yes, to prove that with two fields in the OHTS study they really were or were not progressing, what did you do to change the protocol?

Dr Johnson: We looked to see if it was confirmed, first of all, by retesting, repeated testing. Perform another field and determine if it was in the same location, same shape, and consistent, because sometimes they move around a bit.

Dr Quigley: In clinical practice then, how long would you wait to do the next field? Eve, what are you going to do? You have a patient you think might have progressed.

Dr Higginbotham: In ocular hypertension you can wait a long time, obviously; because they don’t have glaucoma. It is unlikely in six months patients are going to have
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a significant loss. So you can wait six months to repeat that visual field and see the patient perhaps every six months until you have some consistent field experience.

Dr Quigley: What is going to typically push you to do it maybe a little sooner rather than a little later though, Peng? What would you say, "I’d better do it in a month."

Dr Khaw: If they have either extensive cupping or very extensive field loss, then you will have to do it very frequently and very soon, that is to say, within weeks.

Dr Quigley: Or if they are not as clinically stable as you thought. Their target pressure was 15 and they are usually 12, and today they are 16. So you say, now I have two pieces of information that don’t fit well on this patient. Or they had a disc hemorrhage on top of the whole thing. Other corroborating information – now you are going to check the reliability of the field. Chris doesn’t just let any old Joe sell him a field. It has to be a reliable field.

Dr Johnson: This is speaking for the Moorefield’s group, but one of the things they have found is if there isn’t a suspicion factor based on other clinical evidence, one or two visual fields a year is usually sufficient for a glaucoma patient or a glaucoma suspect. If there is an indication, because of a disc hemorrhage or other sorts of things, three fields a year may be useful, but if you do more than three fields a year (and I can’t imagine anyone wanting to do that, either the patient or the practitioner doing more than three fields a year) you really don’t gain any significant information from a clinical perspective.

Dr Quigley: Are you going to get reimbursed for all these fields that you are doing? I think as a physician you have to decide what you are going to do whether you get reimbursed for it or not. It is not very many of the glaucoma patients to whom you would to three fields a year or four a year. I do have a set of people who are getting four fields a year. They are people who, let’s say the endophthalmitis happened after the bleb in the first eye and now they are possibly uncontrolled in the second eye, and they are going “You aren’t going to do that surgery on me, are you?” because they know the possibilities. We would do three or four fields a year to be sure that they actually have a downhill course. As Chris says, you are probably not getting information out of the every three month visual field test and you are only doing it in one eye because you are only interested in that one particular eye.

The other thing that would press you, though, to do the field next week or next month is you just told a patient they might be losing vision. If they are my kind of patient in my office, they are twitching at rest. They are the kind who is on the internet every night looking for the latest information on glaucoma. They know there is a guy in Oregon who is doing this clinical trial, and they are reading me this stuff. They really want to know next week, did their glaucoma really progress or not. A patient suddenly has a much worse visual field one day. They have been pretty stable and they suddenly have a worse field. In fact, it is worse in both eyes. What are you thinking? What kind of history might you take from that patient that day? Mrs Jones comes in one day and her fields are dramatically worse in both eyes.
Dr Higginbotham: It’s a bad day for Mrs Jones.

Dr Quigley: What leads to a bad day for Mrs Jones? My first question to them is what’s going on at home? How are you? These are people you know pretty well. Somebody has lost fifteen pounds, I notice. Did you intend to lose that weight, or how are things going? Because more often than not you hear they have cancer, or their wife died a month ago. A lot of things can effect how well somebody performs at visual field testing. You don’t want to change medicine or do interventions on people because they are in the midst of divorce and they just didn’t feel like sitting there for what? Only six minutes an eye? It can be an awfully hard thing when you are depressed.

Dr Lee: We ask the patients, how do you think you did on the visual field today? They often say, “I really just wasn’t as good today.”

Dr Quigley: The standard comment I say to them, “You really did great on your field today”. Patients don’t think so – they invariably think they did terribly. The field machine makes them feel that way. They are up there playing with threshold. It doesn’t matter how good you are, the machine is fifty percent of the time asking you a question you can’t answer – very frustrating. Tell them they did a great job. Then you say, “You know what? Your field is just as good as it was last time.” Reinforce it for them. Tell them it was not so bad, they really did a good job.

In the average patient… we were talking earlier about the average with structure and function, that on average structure changes before function, but Dr Palmberg found a couple of examples for you of people whose function changed before their structure did, sure. If we start saying the average glaucoma patient doesn’t progress very fast, some of the trial data though suggests to us that there are actually at least two populations of glaucoma patients out there progressing. The vast majority are progressing so slowly the machine wouldn’t ever measure it in their whole lifetime and another group who are going to hell in a hand cart. Some are losing a tenth of a decibel per year and some are losing one decibel per year. At one decibel per year, the average glaucoma patient is going to lose measurable vision. So how do we find those persons? What are the characteristics of persons who are rapid progressers as opposed to those who are just laying low and staying stable? Any pearls there? Can you tell, or you just have to measure their fields.

Dr Higginbotham: I would say you just have to measure the fields. I can think of at least one patient in twenty years who I would say had an exponential loss of vision, but invariably it is more linear and there are small increments, but nothing dramatic. Usually there are patients, perhaps, that have a significant family history and have two or three family members who have had a significant level of blindness, but I would say most glaucoma patients you continue to measure their visual field and examine their optic nerves in a very systemic way.

Dr Johnson: I think I am one step back, because I am still trying to deal with the issue of what is progression. We don’t have a consensus on what constitutes a valid measure of progression in terms of changes in either structure or function. That is an issue that I am still trying to deal with, because worrying about who is more likely to progress or not progress, or what rates, assumes that you know what
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Dr Quigley: Okay, but we are in 2005, it’s February, everybody is going home on Monday, and they have to decide whether their patient progressed. Chris is telling you the honest truth. There is not an established set of criteria for defining glaucomatous progression. There are some clinical trials that have set their own criteria. They decided you had to use a certain number of visual fields to judge progression alone. In none of those studies were fewer than how many fields used?

Dr Khaw: Seven.

Dr Quigley: Yes, the lowest I know of was actually four. One rule of thumb is that if you only have two fields you don’t know if your patient progressed. I don’t care if the second one was worse than the first one. Eve just reassured you that most of them are going downhill slowly, so you don’t have to necessarily make a decision today based on the field alone. Now if your patient has an eye pressure of 47 and has a 0.9 cup, I am not waiting for the fifth field, this is a no-brainer.

Glaucoma management doesn’t always depend entirely on the number of decibels in the upper quadrant. When the visual field test is the only thing changing, I would say that you want to use more than four fields to confirm change. We also know that, and I think Chris would agree, it is a relatively smooth downhill course. If the field is going like this, you need more fields. But if you have a patient who is going downhill fairly steadily in four or five consecutive fields… there are two abnormal points at first and now there are four abnormal points, and there are eight abnormal points, and now there are twelve abnormal points… we don’t have Chris’s definitive decision criteria, but you do have a steady downhill course in four or more fields. Is that reasonable? Would you pick a bone with that? Anybody disagree? That will usually take you between three and four years of follow-up.

How long do you follow your average glaucoma patient between the time they get their first visual field defect and their actuarial death? How long does the average European derived American glaucoma patient have between initial visual field loss developing and death? How long do you have to manage them and keep them from losing vision? I wrote a paper on this subject and it turns out to be about fourteen years. It was a lot shorter time period than I thought it was going to be. Of course, there are glaucoma patients who get initial visual field defects when they are forty, and they have it for forty years. There are people who get it when they are 82 and they die at 83 in their sleep. The average, though, is about fourteen years.

So how many times then… assuming we have a measure of progression… how many actual progressions will you ever measure in the individual glaucoma patient? How many times will the glaucoma patient ever progress? If I am saying it takes four years to prove it, will it be lots of times or not very many?

Dr Higginbotham: Can I make comment for my clinicians? Certainly it’s not feasible for us to do ten visual fields on each of our patients who we think might be progressing. I think that’s where I use some of these optic nerve imaging devices as well as my own clinical exam as a way to actually help to validate or confirm what I think is going on in the visual field. I oftentimes will alternate between imaging a patient and looking at the field as I follow a patient over time. A patient about whom I am very concerned I may see every two months and do one of those two
tests to really determine within a shorter frame time whether or not I think that patient is absolutely progressing. Perhaps that may cut down my number of fields by thirty percent.

**Dr Quigley:** There is another practical reason why Dr Higginbotham does the imaging on one day and the field on another day. Because we all have to take reimbursement into account. Dr Anders Heijl has said that he thinks there might be as many as a dozen steps of worsening that would be measurable in visual fields and Bal Chauhan said the same thing. But that would detect it at a very, very sensitive level, wouldn’t it. When you get very sensitive, you are not going to be very specific, which means you are going to have a lot of false positive guesses. As a clinician, I am not sure that I want to have a lot of false positive progressions on my hands, because it means giving people side effects with medicine and doing ALT’s and trabeculectomies that may or may not be necessary. That takes me to glaucoma progression analysis (GPA).

**Dr Quigley:** Tomorrow, when Chris talks about the glaucoma progression analysis, the new and only progression measure that is on the Zeiss HFA II machine, he will tell you that it is a very sensitive indicator of who is getting worse.

Are you guys using GPA right now? Are you using it at all in your practice?

**Dr Khaw:** No. The question of sensitivity is a critical one. When you look at the Early Manifest Glaucoma Trial, a large number of treated patients progressed. Now if your treatment plan was based upon their criteria, you’d be doing trabeculectomies left, right and center. The fact is, it is a very serious decision to take. Every step forward you take in medication is a big step forward.

**Dr Quigley:** As Chris tells you about this tomorrow, and this is a very well-thought-out program, it looks at two baseline fields and looks at each subsequent one and compares the points to the two baseline fields and tries to give you a good statistical idea of did individual points get worse. One of the problems is the analysis doesn’t tell you that some of the points got better. It doesn’t take that into account. If three points got worse and three points got better, what would you conclude? Nothing happened, right? That’s not what GPA concludes. It concludes the patient is worse, because it ignores the fact that some points improved.

But I think GPA is something useful to look at. Okay, so it’s too sensitive, it still points you to the possibility that a patient maybe going to hell in a hand cart. If everything is fine and stable and you have a very sensitive analysis to judge progression and it didn’t happen, you can feel reassured. My take on GPA is, it is very useful to me when it has not changed, because that patient probably really hasn’t changed. That’s a stable patient. It is very hard for you to do in your head what this GPA does, all this comparison of individual points and numbers; you would need a slide rule and a lot of time to do that analysis in your head.

We have been talking as if we knew what a visual field defect was. What is it that defines on a visual field test the movement from being a non-visual field damaged patient to a visual field damaged patient? What criteria do people use in their practice? Chris can tell us what the criteria were for the Ocular Hypertension Treatment Study. What do you think? Eve, do you have a particular set of numbers or particular thing on the Humphrey field that would alert you and say, I use that all the time, that’s a visual field defect.
Detecting and monitoring progression

Dr Higginbotham: Certainly. Chris could say what they did at the Optic Disc Reading Center, but remember in OHTS, we had the Endpoint Committee that actually validated whether or not we really thought it was a defect. You cannot escape the clinician’s perspective here. I would say first of all, try to be consistent.

Dr Quigley: Yes, but these guys are practicing by committee. These clinicians in this room individually need to know. The committee actually had some recommendations; didn’t you have some official criteria?

Dr Johnson: Yes, I think there is more consensus about detection of early defects. Clustered points that are abnormal are more critical than scattered points in terms of defining early glaucoma. Looking at the superior versus the inferior hemifield, of which the glaucoma hemifield test is a good example, is another issue. I think there are some things that haven’t been looked at that might be helpful, like comparing one eye versus the other. That hasn’t really been done much and that may be quite valuable in eliciting very early changes.

I think Doug Anderson has pointed out something that Rick Lewis and I found as well, which is sometimes people can still be within the normal range, but they start out in the upper end of normal and they go to the lower end of normal. If you looked at that change and they started in the lower end of normal, it would have gone from normal to outside normal limits, but they are still within that population range. I think looking at the individual rather than the population is a good thing to keep in mind and comparing the two eyes. I see that as being room for improvement.

Dr Quigley: Joanne Katz did a study and it was kind of the transition from old Goldmann fields to Humphrey fields. The idea was if you have a Goldmann field defect in somebody, which Humphrey finding best correlates with the Goldmann defect. It was just like going from the old gold standard to the new one. The glaucoma hemifield test being outside normal limits was the single best measure. Your patient can be within normal limits, borderline, outside normal limits, or they can have one of the unreliable things, like abnormal high sensitivity. But when it says ‘outside normal limits’ on a hemifield test and it used to be not bad, it was within normal limits, that is a very reliable thing that the patient has gotten worse. The pattern standard deviation index being five percent or worse is also something that was highly correlated that the Humphrey field was duplicating a Goldmann defect. Chris says three or more clustered points in one-half of the field below or above where they are together and they are all three bad. Paul Foster, Peng’s colleague in London, has written a paper, of which I was a sub-member of the group, about the definition of glaucoma and defines a visual field defect as being three clustered points at the five percent level on the pattern deviation plot (Br J Ophthalmol 86:238-242, 2002).

How many times was the visual field abnormal in the way I just described in the Ocular Hypertension Treatment Study and when the next visual field was done it was normal again? Eighty-six percent of the time it was abnormal and normal when repeated.

This is especially true when it is the patient’s first visual field test. My rule is, if the first field is abnormal repeat it; if the first field is normal, believe it. It is difficult to produce a normal visual field. If you have a patient whose first field is normal, you can believe they have a normal field. Many initial abnormal visual fields will revert to normal when re-tested.
Who is the ideal patient for testing with a SWAP (short-wavelength automated perimetry)?

Dr Higginbotham: I would say the ideal patient is a patient with a large optic nerve, large disc area (megalodisc is another term for that), who has a strong family history and who has already passed the white on white test, that is, they have already done a clean achromatic visual field test before you switched them to the chromatic SWAP test. That would be the ideal patient, and I use it often and I am looking forward to getting the SITA SWAP.

Dr Quigley: Peng, do you use it at all?

Dr Khaw: Yes I do, but again I use it as a sort of early detection radar. If I have a patient who has the sort of risk features that we have talked about, strong family history, very worried, us and them, about them progressing, no overt changes but perhaps maybe some early structural changes, then obviously SWAP acts as an early warning radar system.

Dr Quigley: As the SITA version of SWAP comes on board, you are going to have many more patients who will tolerate doing the SWAP test. Who is the ideal patient for SWAP? Somebody who has an incredible attention span and who really loves you dearly as a physician.

Dr Higginbotham: But they do exist.

Dr Quigley: They absolutely do. Which do you think is more important, a higher eye pressure but a flat diurnal variation, or a lower pressure and much larger diurnal variation in eye pressure?

Dr Higginbotham: That’s a great question. We don’t really have any large trials. We have a couple of retrospective trials that suggest that large IOP variation maybe more detrimental to an eye versus the magnitude of the pressure, but I think that the jury is still out. My guess is that both are going to be very important in the long term.

Dr Khaw: This is an issue that is being addressed, both experimentally and clinically. I have to say my personal feeling is that diurnal variation is very important. The thing about physiological tissues is they don’t like this up and down… you know tissues can adapt to stresses they are under, but if you are constantly changing those stresses, generally biologically tissues don’t take that well.

Dr Lee: Someone asked if I could comment on HRT and the other optic nerve head imaging techniques… you use what you have. I have access to OCT so that’s what I use.

Dr Khaw: I think the real issue is just image with something. A large number of patients aren’t getting imaged at all. That’s much worse than anything else. The fact is you have to image if you are going to look for change because your drawing will never be good enough. I think that’s the real issue.
Detecting and monitoring progression

Dr Quigley: We just looked at the United Health Care data and many of you probably have patients who participate in one of the United Health Care Insurance schemes. There are eight million Americans insured by United Health Care. We looked at the coding for imaging, and I doubt people are doing imaging for free, so I’ll bet when they do the imaging they code for it. Only 13% of glaucoma patients were getting any imaging at all during the follow-up, and this is across a broad regional area from the northeast to the south, to the west.

Dr Higginbotham: I just want to comment that the HRT is being used in seven out of the twenty some-odd OHTS centers. In the near future, we are going to have longitudinal data on the best characterized group of patients at risk for glaucoma.

Dr Lee: I would like to give a comment of caution. I think optic nerve head imaging has some good and bad points. One of the things that happens when you get information from the published literature, not from a sales person or whatever, by the time you have read about it the instrument has changed at least once and sometimes twice, so it’s not the same machine that obtained the published data. That’s something to keep in mind – what has undergone peer review versus what is mentioned by a salesperson as the latest and greatest and hasn’t been independently verified or documented.

Dr Quigley: SWAP is affected by cataract. How did you address the cataractous effect on a blue target?

Dr Johnson: That was something that came up both for Pam Sample and the UC San Diego group and our lab. We found that localized types of deficits were really the important factor critical in SWAP. The cataract causes a diffuse type of loss and by subtracting out the diffuse loss and paying attention to localized components such as localized nerve fiber bundle type patterns, things of that nature, we were able to extract out the relevant glaucoma-related data. I don’t think it has completely solved the problem, but I think this is one way to deal with it.

Dr George Ellis Jr: It is a little confusing to me... of course I don’t deal with adults, so maybe that is part of the problem. If you have a disease that only lasts fourteen years from diagnosis until death and it takes four years to show progression, should these people be treated with benign neglect?

Dr Quigley: One of the most senior people in glaucoma, somebody who I think each of us on the panel would say we have the greatest respect for in terms of experience and knowledge of glaucoma is Stephen Drance and the second person, I would say who I have the greatest respect for is my former fellowship advisor, Doug Anderson. After doing the Normal Tension Glaucoma Study, the two of them wrote that few patients, even those who had already progressed once, progressed again in that study with glaucoma at normal pressure. So few people got worse that it probably would make sense to wait for somebody to progress before ever treating them in the first place. Now that’s an academic approach. I think if you have ideal circumstances, you have a patient who is a reliable field tester, you have a person who would prefer not to be treated, that you can watch people like that, and I just did that with the chairperson of a department at the Hopkins School of
Public Health who, as an epidemiologist, had read all Chris’s papers and everything else, and he said, “I have read this statement by Drance. He thinks we shouldn’t be treated.” So we spent two and a half years and during that time he did progress with visual fields getting done every six months and now he is on eyedrops. I don’t know whether that’s the best choice for Americans in general. It is certainly not unreasonable as an academic assumption based on what we know about information. I think you and your patient have to make that choice based on the information you have.

**Question from Audience:** Could you comment on the effect of the yellow lenses from Alcon on the SWAP perimetry?

**Dr Quigley:** On the intraocular lens that has an additional blue blocker in it, right?

**Dr Johnson:** My feeling is, that it is not really much worse than the naturally occurring lens which is in and of itself a blue blocker, because you are losing a lot of short wavelength light from the normal lens. If you have a filter over an intraocular lens, I don’t think that is much different than the normal condition. I don’t see it as being a distinct disadvantage for SWAP.
Anterior Segment Surgery
Toxic anterior segment syndrome

James Gills

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In this paper I will present a case of toxic anterior segment syndrome which has influenced my use of intraocular lidocaine. Toxic anterior segment syndrome (TASS) is characterized and distinguished from endophthalmitis by early onset, profound corneal edema, a fixed dilated pupil, significant iris atrophy, intraocular inflammation with possible hypopyon and elevated intraocular pressure (Fig. 1). A number of possible factors and agents have been associated with TASS, for example: intraocular lenses, contaminated BSS, intraocular antibiotics, bacterial endotoxins and residue found on intra-operative instruments.

Fig. 1. TASS with marked corneal edema and a dilated fixed pupil.

Our experience with TASS suggests a strong association with the use of intraocular lidocaine. All of our cases occurred in patients who received topical lidocaine anesthetic and intraocular lidocaine 1%. A cluster of cases occurred when
we began using extra lidocaine 1% for hydodissection of the nucleus. In these TASS cases, we were using a full 1 ml of intraocular lidocaine 1%.

One case followed the rotation of a toric lens where lidocaine 1% was the only intraocular fluid injected. The case involved a 71-year old man who underwent an initial cataract surgery and was doing well. Following the repositioning of his toric lens with intraocular lidocaine 1%, he developed TASS. He subsequently developed glaucoma not controlled by medications or Ex-Press valve surgery. The patient went on to have an Ahmed valve and penetrating keratoplasty (Fig. 2). His final visual acuity is 20/25, with a restricted visual field.

Early treatment of TASS with topical steroids appears to enhance patient outcome. Because of our experience with a cluster of patients with TASS following the additional use of lidocaine 1% for hydodissection, we have changed our surgical technique. We now inject 0.5 cc lidocaine 1% into the AC and prior to making the capsulorhexis. We no longer use additional lidocaine for hydodissection. Since making this change, we have not had any cases of TASS.

We believe there were two main causes of TASS in our patients: we used a higher dosage in some cases than our typical 0.5 cc, and the Xylocaine remained in the eye for a longer period of time. We applied this technique of instilling a slightly higher dosage and longer contact time following reports of diminished capsular opacification with Xylocaine.1 It was during this time that we experienced our cases of TASS.

The severity of the toxicity was rather broad, ranging from diffuse corneal edema, the intractable glaucoma and one case required a corneal transplant. All patients had diffuse corneal edema.

It is my conclusion that the spectrum of toxic reactions is related to dose and contact time. After we reverted back to normal dose and contact time, we had no cases of toxicity in 20,000 eyes.

References

Questions and Answers

Presiding Physician: Barry Leader, MD

Dr Barry Leader: What is your approach to using prostaglandins in eyes having glaucoma and cataract surgery?

Dr Singh: I tend to not stop them before the surgery and I usually will not resume prostaglandin use for several weeks to several months after the cataract operation. For a patient on a prostaglandin as a single agent, following cataract surgery I will see what the pressure does, because sometimes cataract surgery alone will result in a reduction of IOP and they don’t need their medicine anymore. If they do need something in the perioperative period, I generally will give them an aqueous suppressant, beta blocker, sometimes an alpha agonist, and wait an average of at least a month before I will start the prostaglandin again. Long term, I may put them back on the prostaglandin, but it is surprising how many people don’t need medication after having a cataract operation.

Dr Gills: Ditto.

Dr Leader: Several questions for you, Dr Gills. Have you noticed an increased incidence of endophthalmitis following cataract surgery with current incisional techniques?

Dr Gills: In 1992, I did a study showing that the eye pressure drops for about twenty minutes following cataract surgery and you have to really construct a watertight wound.

Dr Leader: Dr Gills, with intraocular Kenalog, even at a 0.4 mg dose, there is a real problem of IOP increase even six months after an injection. Why subject your patients to such a risk?

Dr Gills: I was very concerned about the risk of steroid induced glaucoma. We aren’t getting glaucoma at these low doses.

Dr Leader: What is your dose again of the Kenalog?

Dr Gills: We use about 1.5 mg. We don’t get much rise in IOP. We occasionally do and usually treat it medically and it goes away.

Dr Leader: Dr Gills, are you concerned that the use of intraocular steroids may mask endophthalmitis?

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edited by Jonathan D. Nussdorf
Dr Gills: I am concerned, I have been using intraocular steroids and non-steroidals for so many years and our rate of endophthalmitis is about one in 25,000, it’s hard to say it’s so rare. What bothers me is having a patient develop cystoid macular edema (CME) and you’re going to have clinical CME one or two percent of the time. That’s the biggest problem, dealing with those CME patients, not the endophthalmitis patients. I just don’t see many endophthalmitis patients.

Dr Leader: Dr Gills, do you reconstitute the Kenalog in any special way?

Dr Gills: We went through this, as did the people in Europe and found out there was no reason to. We don’t do anything; we just mix it up and we try to get it so the approximate dosage is about 1/40 of what is in the bottle. It is a 10 to 1 of what touches the cornea. You can find some information at our website www.stlukeseye.com.

Dr Quigley: I wanted to ask Kuldev about target pressure; because I think what you heard from Dr Singh was a very nice presentation of what could be wrong with the concept of the target pressure, but perhaps not quite as balanced on what’s right with it. Among other things, there are already legal cases in which doctors who didn’t have a target pressure mentioned in the chart, at least a range, for not following the practice patterns of the American Academy of Ophthalmology. While you may in fact be at some risk if you write a target pressure in your chart and you are not achieving it and you don’t comment that you’re not achieving it, you are actually much worse off not having any comment in the chart at all, I believe. This is personal clinical judgment between the two of us.

I wanted to ask Dr. Singh, you have a patient whose pressure is 18 and you decide to treat the patient with a unilateral trial of Xalatan and the patient comes back and the pressure is 15. How do you know whether you have achieved something if you didn’t make a decision about a target range?

Dr Singh: Well, I think it is just a difference in philosophy. First of all, to address the concept again, the problem I had with the target IOP is that it is a moving target. If you have a target and are not flexible with that target, then you are not using all the information you have available. This is more of a philosophical difference. In real life, I would probably do the same thing Harry does. I have a target in my mind and I write down what my goals are in the notes, but I don’t put it on the side of the chart saying this patient has to get to this level or I am not happy. You have to look at the cost of therapy. If you have set the pressure but if you don’t look at what you need to get to that pressure, you’re not going to make good decisions. What you are doing to get to that target pressure is more important or at least as important. I probably didn’t answer your question Harry. But the point is, with that patient that went from 18 to 15, I would probably continue to treat him.

Dr Quigley: In the old days, people normalized the eye pressure and that’s not therapy any more, so we have to have some idea of did we succeed with our unilateral trial and for that reason you almost have to have a number in your head of what that target range is and my argument is simply to write it down and I agree, be flexible. Change it, erase it, write down a new target.
Dr Singh: I think I agree with that. I just have to make a thirty second rebuttal to Harry’s earlier comments weighing on my mind. On the target IOP, what I generally go for is mid teens, high teens, or low teens. I have an idea of where I want the pressure to be, and that’s about as specific as I get.

Dr Leader: Dr Singh, are you a proponent of one eye trials.

Dr Singh: I am. But I have to be honest with you. I don’t do a one eye trial on the majority of my patients who present with glaucoma. I tell them to take the medicine in both eyes and I send them home and see what happens. You might ask, “How can you be a proponent of one eye trials?” I think the one eye trials are more useful in other situations, for instance taking people off therapy and for trying different adjunctive agents in different eyes, switching therapy in one eye and leaving them on the old therapy in the other eye.

A recent article by Realini and colleagues has questioned the use of one eye trials because the pressure in the two eyes are not correlated. I’d like to see a confirming study of that because we have always been taught that it was a useful thing to do and technically you should do a one eye trial on everybody; just practically I don’t perform one eye trials on all new patients.

Dr Palmberg: I think the Realini papers are not helpful in understanding one eye trials. First of all he says he doesn’t think a one eye trial makes sense because his first paper said the two eyes could differ from each other of about 3 mmHg. We are using drugs that change can change IOP 6 to 9 mmHg. That should make one eye trials worthwhile. Second, in a retrospective study, Realini showed that following a one eye trial, pressures came down 5 mmHg in that one eye and then the other eye dropped 2 mmHg when drops were added to that eye. If you have retrospective data and the pressure comes down 2 on Xalatan, it doesn’t sound like the patients are taking the medicine or this is an informative study. The real data is going to come out of the ocular hypertension trial where a one eye trial was performed on 800 people and then the other eye.

Dr Singh: I agree, making the general statement that the one eye trial is useless based on that paper is not correct.

Dr Leader: Any other questions or comments?

Dr Quigley: It’s concerning Dr Gills’ use of intraocular steroids. Jim showed you a picture, and it was a picture of Kenalog in the stroma of the iris.

Most of you are probably not aware that fluid in the iris goes in like a sponge. The iris stroma actually has a lot of open spaces in it. You know that sort of looking at the slit lamp, you see the ropey stuff. Jim, this is something we’re studying at the very moment as it may relate to angle closure glaucoma. It turns out the iris of the eye, when it is in the small pupil position, has a certain area. You can imagine the cross section of the iris. When the iris dilates and the pupils is now 7 mm, the area of the iris dramatically gets smaller, because the fluid within the stroma of the iris leaves like you’re squeezing a sponge. You have a beautiful example of it with your Kenalog of how much fluid is within the stroma of the iris. Could it be a risk factor for angle closure glaucoma that some people’s iris is less spongy than
the others so that when it dilates it is more likely to occlude the angle than not? We are studying that right now by putting a tracer into the stroma, just like your tracer of Kenalog.

Dr Leader: Thank you all very much.
Laser trabeculoplasty – background, mechanisms, clinical applications

Robert Noecker

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Introduction

Argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) are procedures used by the ophthalmic community as alternatives to medical therapy for the treatment of glaucoma. ALT has been used for over a quarter century, while SLT is relatively new to the US receiving FDA approved in 2001. Both laser procedures are employed to lower intraocular pressure (IOP) in eyes with open angle glaucoma by causing changes in and around the trabecular meshwork (TM). Both procedures produce roughly equal IOP reduction. However, the two procedures are markedly different in the amount of laser energy administered, the type of laser-tissue interaction that occurs, the timing of IOP response after the procedure is performed, and patient comfort during the procedure. This paper will compare and contrast the similarities and differences of these two techniques, and address the strengths and weaknesses of both.

ALT was first described by Wise and Witter, in 1979. At the time, given the paucity of effective or tolerable medical therapies, ALT gained widespread acceptance as a treatment for open-angle glaucoma in a short period of time. Latina introduced the concept of SLT after finding that the laser caused a drop in IOP in monkeys instead of raising it in an experimental setting (personal communication). After cell culture work and experience in clinical trials, efficacy was demonstrated in humans, and the procedure has gained increasing acceptance in recent years, replacing ALT in situations in which SLT is available.

The lasers

ALT is performed with an Argon laser, a gas laser that emits green light at the wavelength of 514 nm. It is traditionally a water cooled laser that requires signifi-
cantly plumbing and electrical equipment and is non-mobile due to a relatively fragile structure. The same procedure has been performed recently with double frequency Nd:YAG lasers which emit light at 532 nm. These newer, solid state lasers are portable, and less expensive than traditional argon lasers. These lasers can deliver light for variable amounts of time, the shortest pulse duration is typically 0.01 seconds. The spot size of the laser application is also variable, ranging from 50 microns to 500 microns in diameter. The energy that can be delivered ranges from 10 milliwatts (mW) up to several watts of power.

The SLT uses a double frequency Nd:YAG laser that also emits a green wavelength of light at 532 nm. It is a solid state laser that is compact and is easily portable. The SLT laser is Q-switched which limits the pulse duration to 3 nanoseconds (nsec). The spot size is also fixed at 400 microns diameter. The energy that can be delivered is relatively low, ranging from 0.1 millijoules (mJ) per pulse to 2 mJ/pulse.

The SLT pulse duration is similar to that used for Nd:YAG capsulotomies and iridotomies, resulting in a ‘cold’ laser application without heating of adjacent tissues. However, the green wavelength associated with the SLT is well absorbed by pigmented tissues making it ideal to target the trabecular meshwork, which contains pigment at the cellular level in all patients. However, the spot size is larger at 400 microns versus 10 microns for Nd:YAG capsulotomies and iridotomies. Therefore, there is no plasma formation or significant disruption of structures at the supracellular (trabecular beams) level. While the SLT and argon lasers operate at similar wavelengths, the SLT with its shorter pulse duration and large spot size produces different laser tissue effects when compared to ALT.

**Treatment parameters**

For both treatments, the patient is seated at the laser’s slit lamp assembly and a drop of anesthetic is applied to the eye. A gonioscopy lens with a viscous artificial tear gel is applied to the eye. Any gonioscopy lens that does not magnify can be used, a Goldmann lens is most commonly implemented.

ALT laser settings are argon green wavelength; spot size 50 microns, power setting between 500 mW and 1000 mW and duration of 0.1 seconds. The laser spot is brought into focus at the junction of the pigmented and non-pigmented trabecular meshwork (Figs. 1 and 2). The clinical treatment endpoint is whitening of the trabecular meshwork with a single transient small bubble formed at that point within the trabecular meshwork. The initial treatment covers between 180 to 360 degrees of the angle. The burn spots are spaced 2-3 apart or about 50 spots for each 180 degrees of treatment. There is residual blanching evident in the pigmented trabecular meshwork after treatment that helps to guide the physician. Two sessions, each consisting of 180 degrees of treatment, can be carried out so that a maximum of 360 degrees of trabecular meshwork is treated.

SLT uses light at 532 nm, with a spot size of 400 microns, pulse duration of 3 nsec and energy starting at 0.8 mJ and titrated up or down depending on the clinical response. The clinical endpoint of treatment is ‘champagne bubble’ formation, with wafting of the bubbles into the anterior chamber. The goal is to treat at this ‘champagne bubble’ threshold; treatment levels that do not produce bubble
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Fig. 1. Gonioscopic view of ALT (Arrow head) and SLT (Arrow) treatment spot size and placement. (Courtesy M. Latina, MD.)

Fig. 2. Comparison of ALT and SLT spot size on the trabecular meshwork.

formation may not deliver the maximal effect whereas operating well above bubble formation threshold, may lead to unnecessary inflammation and IOP spikes. The treatment is performed so that, on average, a total of 100 applications are delivered across 360 degrees of trabecular meshwork (Figs. 1 and 2). The spots are abutted in order to fit approximately 100 over the entire angle. The laser spot covers the entire angle, frequently covering some of the peripheral iris and cornea. Typically, there is no evidence of areas of prior treatment, so the operator must use other landmarks to keep track of the treated areas.
Tissue interaction and mechanism of action

As with argon laser treatment in other parts of the eye, ALT has a significant thermal effect. The pigment containing structures absorb the light energy and convert it into heat energy, therefore causing localized damage to the target tissue. In the case of the trabecular meshwork, both pigmented TM cells, as well as non-pigmented TM cells are affected (Fig. 3). In addition, other structures such as the trabecular beams are heated, resulting in coagulative damage around treatment areas which cannot be repopulated by TM cells.2-5

![Image of human TM (organ system). ALT 50 µm spot. Coagulative damage as seen with ALT. In vivo, scarring will eventually occlude this area of the trabecular meshwork.]

In contrast, SLT operates on the property of selective thermolysis. The requirements for selective thermolysis to occur are: (1) intracellular target chromophore (melanin) and no competing chromophores are present; (2) the target tissue must absorb laser energy better than surrounding tissues; and (3) the characteristic short laser pulse is sufficient to generate heat within the confines of the cell. Only pigmented cells within the irradiation zone will be targeted. Heat diffusion is limited, because the light pulse duration is below the thermal relaxation time of the target.6

In theory then, the characteristics of the SLT light pulse targets the pigment containing TM cells that are more abundant than all other surrounding pigment cells and structures.7 This process is possible due to the short pulse duration of the laser light set at 3 nsec. This duration is less than the thermal relaxation time of biologic tissues, which is about 10 nsec. As a result, the laser energy is withdrawn before heating of the surround tissues occur and therefore, coagulative damage is not seen (Fig. 4).

The mechanical theory of how laser trabeculoplasty lowers intraocular pressure posits that the TM cyto-architecture becomes distorted. The photocoagulative effect of the laser energy causes the spaces between the trabecular beams to be stretched or blown open. This mechanical theory of trabeculoplasty has been
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Touted for decades, but more recent work investigating the biological processes induced by ALT has called this into question. In addition, the fact that SLT produces a pressure lowering response with less tissue distortion detracts from a pure mechanical explanation of laser trabeculoplasty. The biological theory postulates that a series of chemical and biological events take place after laser treatment and better explains the intraocular pressure lowering effect of both SLT and ALT.

Evidence suggests that upon absorption of a laser pulse, cells are stimulated through a process of biophotoactivation to produce a cytokine response. This cytokine response leads to the recruitment of macrophages and modification of the extracellular matrix. The induction of metalloproteinase activity and macrophages helps to clear extracellular debris. The biophotoactivation of trabecular meshwork cells leads to improved outflow facility across TM and lowers intraocular pressure.

Clinical studies

Initial studies on ALT showed that the procedure reduced IOP by approximately 25%, with a successful response in approximately 75% of patients. Success rate is generally higher in older patients than in younger patients, but there are exceptions. Younger patients with pigmentary glaucoma tend to respond well to ALT, and ALT is also effective in lowering IOP in pseudo-exfoliation syndrome glaucoma. Its efficacy in the treatment of some of the secondary open-angle glaucoma is variable. ALT is less effective in the treatment of angle-recession glaucoma and, in some cases, can actually raise IOP levels.

The duration of action of the IOP-lowering effect of ALT is limited, with at least one early study demonstrating that the mean duration of effect of ALT in Cauca-
sians to be about five years and less in African Americans. In pseudo-exfoliation syndrome glaucoma, the duration of action has been found to be briefer, with many patients having IOP return to pre-treatment levels within 1.5 years to 2 years.

ALT as initial treatment for open-angle glaucoma was studied in the Glaucoma Laser Trial (GLT), a multi-center clinical trial sponsored by the National Eye Institute (NEI). The GLT study evaluated 271 patients with previously untreated primary open angle glaucoma and whose eyes were randomized to receive either primary ALT or medication. Patients had one eye initially treated with ALT, while the fellow eye was started on medical treatment. The majority of patients were followed for seven years. Through the first two-year follow-up, ALT eyes had achieved an average lower IOP than medication-treated eyes; 25% of ALT treated first eyes did not require medication. At seven years, in 203 of the original 271 patients, ALT-treated eyes had lower IOP, better maintenance of visual field and optic disc status as compared to eyes in the medication first group.

At the end of the study, no statistically significant differences existed between the eyes initially treated medically and those initially treated with ALT. Although not statistically significant, slightly fewer of the eyes treated with ALT required filtering surgery, and visual field status in those eyes changed slightly less than in those treated with initial medical therapy. The study was limited in that it did not account for potential cross-over effects of the ALT or eye medications. In addition, the sample size was small and the follow-up was variable. Another limitation of the GLT study was that it involved patients with early glaucoma from a relatively homogeneous population. At the conclusion of the study, a majority of patients eventually required the addition of topical medications to the initially laser treated eye.

A second NEI sponsored multi-center clinical trial, the Advanced Glaucoma Intervention Study (AGIS), compared the use of ALT with filtering surgery in more advanced glaucomatous eyes that were uncontrolled by maximum tolerated medical therapy. Follow-up during this study was as long as 13 years. The AGIS found that filtering surgery tended to lower IOP more than ALT and that more of the eyes initially treated with ALT required a second intervention than those initially treated with surgical trabeculectomy. The study also found that in African Americans, the visual acuity and visual field results were better in eyes treated first with ALT than in eyes treated first with trabeculectomy. In the Caucasian population, the opposite was true.

It is important to note that both the GLT and AGIS clinical trials were conducted prior to the availability of topical prostaglandins, topical alpha-2 agonists and topical carbonic anhydrate inhibitors. Prostaglandins are potentially more effective at lowering IOP and have fewer side effects than the medications used in the GLT. As a result of the availability of these additional topical agents during the 1990s, ALT decreased in popularity.

The efficacy of ALT and SLT is similar. In a pilot study by Dr Latina and colleagues, SLT was used to treat 53 eyes with primary open-angle glaucoma on maximum tolerated medical therapy, with 70% of those eyes responding with a 3 mmHg or greater reduction in IOP. In this study, baseline mean IOP was 24.6 mmHg and the mean IOP lowering response was 23.8% (Fig. 5, square symbols). Adverse events including anterior chamber reaction 90%, pain (5%), redness (5%) and IOP spikes greater than 10 mmHg (2-5%). Based on this study the FDA ap-
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proved the laser for the treatment of open angle glaucoma after failed medication use and after failed prior argon laser trabeculoplasty.

Damji et al. performed a prospective randomized clinical trial designed to compare the IOP lowering efficacy of SLT vs. ALT in patients with uncontrolled primary open-angle glaucoma (POAG).11 The patients in this study were on maximum medications. The primary outcome was the intraocular pressure measured at one year and the secondary outcomes were: anterior chamber reaction, cell and flare each graded on a scale from 0 (normal) to 4+ (marked reaction) and Snellen visual acuity. An attempt was made to keep patients on a constant regimen of medication during the study period. They reported three-year follow-up data and found that the number of medications used at each visit was comparable between the two groups. The percentage of eyes that achieved 20% or more IOP lowering was 72% in the SLT group and 61% in the ALT group.

Francis and colleagues presented a prospective interventional trial of SLT as a replacement for medical therapy in patients with controlled primary open-angle glaucoma (POAG) or pseudo-exfoliation glaucoma at the 2003 American Academy of Ophthalmology meeting.12 They evaluated 112 patients across three groups. Group A: no medical therapy (n = 18); Group B: controlled on medical therapy (n = 66); Group C: uncontrolled on MTMT (n = 28). The primary outcome for Groups A and C was IOP at six months and for Group B a decrease in number of medications. The secondary outcomes were anterior chamber reaction, visual acuity, pain. The authors found IOP reductions of 26% in the unchanged medication Groups A and C and average reduction of one medication at six months in Group B with maintenance of IOP in an acceptable range.

Melamed and colleagues evaluated SLT as primary therapy in a prospective, non-randomized study. In 45 eyes, with 12-month data, they found an average 7.9 ± 2.5 mmHg (30.0%) IOP reduction after one year.13 Other studies have indicated a mean IOP reduction of as much as 35%.14

The Glaucoma Laser Trial established ALT as a viable initial treatment alternative to medications. Currently, the multi-centered, randomized SLT/MED study is underway to determine SLT’s efficacy as an initial therapy alternative to medica-
tions. Because of the obvious similarities between ALT and SLT, the initial treatment parameters for the SLT trials for FDA approval of the device were based upon the treatment parameters used for ALT. However, experience in the SLT/MED study and results from recently published study have shown that SLT of the entire angle can be performed without significantly increasing the risk of sustained pressure spikes. Without medical therapy pre-treatment, the post-laser IOP spike rate can be >30% for ALT and 20% for SLT. However, pre-treatment prophylaxis with an alpha-2 agonist the IOP spike rate for both decreases to less than 5%.

In the SLT/MED study, a group of experts developed a protocol based upon evidence and experience. This trial is being conducted at 16 sites in North America. Patients are randomized to either a structured ‘best practice’ medical treatment algorithm beginning with prostaglandin analogues or SLT. Three hundred forty patients are enrolled for this 18-month study. Both eyes are treated within two weeks with 100 pulses over 360° of the angle. If pigmentation grade is 1 or 2, 0.8 mJ is the starting energy – this is titrated according to target tissue response and the appearance of ‘champagne bubbles’ wafting into the anterior chamber.

Based upon the SLT/MED protocol and experience, there are a few patient treatment scenarios when complications or less than ideal outcomes with SLT may develop. Large IOP spikes may occur in patients with pigmentary glaucoma and initial treatment in that population should be limited to 180° or less. The pigment in this condition is mostly extracellular. Therefore, a tremendous amount of pigment may be disturbed without the laser energy getting to the target tissue, the pigmented trabecular endothelial cells. For this reason, in the SLT/MED study, patients with heavy pigment grade 3 or 4, the starting energy level may be as low as 0.4 mJ. Depending on tissue response and pigment in angle, the energy is increased or decreased by 0.1 mJ increments to a maximum of 1.2 mJ and a minimum of 0.3 mJ.

**Practical points for performing SLT**

My SLT pretreatment regiment includes one drop each of brimonidine purite to blunt a post-laser IOP spike and proparacaine as topical anesthetic. I use Gentec gel as a coupling agent for the contact lens. It is important to use a contact lens with no magnification (1X), such as a Goldmann 3 mirror. Changes in magnification will alter the beam diameter and energy distribution. Initial laser settings are duration of 3 nanoseconds (preset), a spot size of 400 microns (preset), and an energy level of 1.0 mJ/pulse. I aim to cover the angle (not the iris) and plan to treat the entire 360 degrees (100 applications total or 25/quadrant) with the laser applications abutted. It is desirable to see ‘Champagne bubbles’ moving into anterior chamber frequently. I do not want blanching or large bubbles and I adjust the energy up or down accordingly. I avoid areas of PAS and the iris as treatment to these structures will cause discomfort. The aiming beam is directed over the trabecular meshwork and the lens is rotated to cover TM. When treating with SLT, physicians should think of the task to be that of exposing or painting the trabecular meshwork rather than causing focal burns.

My post-treatment regiment includes brimonidine purite one drop, ketorolac one drop and the IOP is checked at post-op one hour and treated accordingly.
Postoperative treatment usually consists of topical NSAIDS, as steroids may have a negative effect on macrophage migration and function, which are essential to incite the increase in outflow facility. Patients are sent home with ketorolac one drop four times a day for four days and are seen for follow-up in 10-14 days. Longer term follow-up usually occurs at six to eight weeks to determine full effect of the laser treatment.

A poor initial pressure lowering response at six to eight weeks suggests a poor prognosis for re-treatment. Re-treatment can be done if an initial favorable response fades. Re-treatment can be performed as soon as six months to years later. SLT appears to work independent of other procedures.

Patients appropriate for SLT include those with open angle glaucomas: POAG, pigmentary, pseudo-exfoliation, juvenile, and angle recession glaucomas. Other criteria include those who are poorly compliant with their medical therapy, intolerant or unresponsive to medical therapy, those who have had failed ALT (either 180° or 360°) or have failed glaucoma filtering surgery.

In the past, my initial protocol was to limited treatment to the 180° inferior angle. I now routinely treat 360° TM with improved patient response and IOP lowering. However, for patients with pigmentary or pseudo-exfoliation glaucoma, I limit initial treatment to the inferior 180° TM. The amount of pigment present in the angle influences the energy setting; more pigment present tends to require less energy to produce a therapeutic effect. In these patients, treatment is started with 0.8 mJ, adjusted to produce bubbles every few pulses.

ALT vs. SLT

ALT is safe and simple with few ocular side effects and, although mild inflammation in the eye is possible for a few days or a week after the procedure, it usually does not affect vision or have any long-term negative effects on the eye. Ten percent of patients have had an acute pressure rise of 10 mmHg or more immediately following ALT, but pre-treatment with apraclonidine HCl 0.5% eliminates this pressure rise in most patients.

In 2001, SLT became available in the US. SLT has been touted as being superior to ALT because of the reduction in thermal damage to the trabecular meshwork. There are distinct differences in collateral damage and side effects of ALT and SLT. SLT causes a minimal amount of damage, which is limited to pigment containing trabecular cells. The higher amount of laser energy used in ALT, applied for longer durations of time, results in heating and subsequent coagulative tissue damage beyond the treatment area. This can lead to permanent structural damage and scarring of the trabecular meshwork. No such structural damage occurs with SLT due to the short pulse duration of three nanoseconds and lower energy requirements (1 mJ/pulse).

Most studies comparing ALT to SLT show virtually identical efficacy in lowering of IOP on initial treatment. Because of the lack of structural damage, treatment with SLT is potentially repeatable. Anecdotal experience supports this, although larger scale studies have not yet been completed. Some of the studies using SLT in eyes previously treated with ALT suggest that SLT might lower IOP with re-treatment, whereas repeated ALT does not, or does so to a lesser degree.
SLT marks an advance in the treatment of glaucoma. It is a safe procedure that is not limited by collateral damage to the outflow structures of the eye. The procedure is more comfortable for the patient compared to ALT and is unique in the amount of energy it delivers to the trabecular meshwork.

References

How to stay out of trouble managing trabeculectomies

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Introduction

Primary surgery for glaucoma is presently dominated by trabeculectomy, and there are as many methods for this procedure as there are surgeons. The purpose of this description is to put the author’s personal experience with 3,000 such operations in the context of practical suggestions for management. While most trabeculectomies are successful, or at least uncomplicated, there are methods that can maximize the chance that the most serious complications are avoided.

Indications for trabeculectomy

There are several reasons for performing the procedure. These include:

- Failure of eyedrop medication to reach the target pressure
- Failure of laser trabeculoplasty to achieve the target
- Poor taking of eyedrops
- Inability to pay for eyedrops
- Patient preference for surgery over other treatments

Indeed, surgery as initial treatment for glaucoma was evaluated in the Collaborative Initial Glaucoma Treatment Study (CIGTS). As a means of achieving the target pressure, surgery equaled or exceeded eyedrop therapy. The cost in terms of reported symptoms from the patients were surprisingly high – with equal discomfort to that experienced by those taking drops for at least the first year after surgery. Yet, the visual field was at least as well preserved by surgery as by medical therapy, and it can be argued that the effectiveness of surgery would be even higher in general practice, where the adherence and persistence with medical therapy are known to be much lower than was the case in a highly controlled clinical trial population. If these conclusions are generally applicable, then why has there been no mass movement toward initial surgery?

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There are several serious complications of trabeculectomy that probably inhibit more frequent use of initial surgery. These include bleb dysesthesia, astigmatism, cataract, hypotony, and bleb-associated endophthalmitis. In this report, I will summarize some anecdotal observations that may be of use to others who perform the procedure.

Bleb-related discomfort

As many as 20% of those who undergo trabeculectomy have symptoms from the procedure that are described (if elicited) beyond the immediate six-week postoperative period. These derive from the fact that the bleb is either high enough, anterior enough, or spreads around the limbus enough to disturb the normal motion of the lid in surfacing the cornea with tears. Blebs can, when running all around the limbus, project through the lids or block the lacrimal punctum. The big bleb typically becomes smaller with time. However, artificial tear drops and ointment are often needed to alleviate discomfort. Night or even daytime patching with a shield at night to avoid pillow contact with the eye may be useful. When the symptoms are unremitting, particularly when dellen form anterior to the bleb, a repair in the form of bleb reduction is indicated. It has been my experience that NONE of the non-surgical methods for bleb reduction succeed often enough to even try them. These include large contact lenses, blood injections, compression sutures, and scarification with laser and caustic chemicals.

The best defense is a good offense, so it is wise never to center a trabeculectomy operation closer to the horizontal meridian than either 11 or 1 o’clock. Please don’t perform it at 12 o’clock, since this ruins the chance to do a second trabeculectomy on the same eye (remember the success rate is at best 80%, so you will need a second site 20% of the time if you live in the same town for any period). Some surgeons believe that fornix-based conjunctival flaps are less likely cause big blebs than limbus-based flaps, and that the big bleb is potentiated by performing Tenonectomy. My experience is that it is equally easy to get too big a bleb with either type of flap, and comparison of the rate of big blebs in large series with and without removal of Tenons also does not support this as a direct cause. It seems to be related to, as yet, unknown features of individual patient healing.

Second, large blebs can often be brought to smaller size with pressure-lowering eyedrops (the type is immaterial). This is obviously important in the high-domed bleb phase with intraocular pressure (IOP) above the normal range. These can frequently succeed and even have the drops stopped at 3-6 months after initiation of therapy.

When the large symptomatic bleb is unresponsive to waiting, the method(s) for bleb reduction are straightforward, with the chief steps being to remove a substantial portion of the offender and resuture the cut edge firmly to the cornea. I do not disturb the filmy connective tissue that overlies the scleral flap in these cases. The leading one-half of the bleb should be excised with a sharp blade from limbus to limbus. The remaining conjunctival tissue requires dissection from episclera – typically with a blade, as scissors are too likely to tear the tissue. When the conjunctiva has been freed sufficiently to allow it to be advanced to the limbus,
it is sewn in place with two interrupted 10-0 nylon sutures that pass parallel to the limbus just into the cornea, through the conjunctiva and have knots buried. I do not use mattress or running sutures here, as these most often cause the tissue not to sit flat (and frankly, they are not needed in most cases). When the conjunctiva is too rigid to advance from the fornix, an incision in the fornix can be made, moving the conjunctiva as a bridge attached laterally (as in a Gunderson flap). After suturing at the limbus, the posterior margin can be sutured to episclera with 9-0 vicryl interrupted suture. Occasionally, I have constructed a pedicle flap of conjunctiva from either nasal or temporal and swung it into place over the area. This is complex, but far preferable to a previous technique, the free graft of inferior conjunctiva. The latter is satisfactory initially, but often leads to a progressively thinner bleb tissue due to the lack of any blood vessels that come with the graft (and none grow into it).

For the bleb that runs down and around the limbus, an area of conjunctiva of at least two clock hours should be excised and the area left bare to epithelialize later. The cut edges are sewn to episclera with interrupted 9-0 vicryl suture and a BV-100 needle that makes only tiny holes in the tissue. This should be done with the buried knot technique, the needle passing up through one side of the margin, down through the other, and the knot left under the tissue so that the patient does not feel the knot ends for 2-3 weeks. The 10-0 nylon ‘wing’ sutures that hold the conjunctiva at the limbus typically remain buried for years, though about 25% of them become loose and can be easily removed at the slit lamp. It is amazingly difficult to ruin a bleb with bleb reduction (or after repair of a leak). Over 90% of those blebs that we have re-operated retain the target IOP, most of them without eyedrop help.

**Astigmatism**

While seemingly trivial, astigmatism after trabeculectomy can be a bothersome issue. Most often, this is a positive cylinder in the spectacle correction in the axis parallel to the position of the scleral flap and can be 2-3 diopters initially. Our supposition has been that it is due to cautery of the sclera. Cutting or release of the scleral flap sutures does not improve the warping. It does fade over the year after surgery, but for the previously emmetropic patient, it is a nasty surprise that “my vision is terrible since that operation”. For the post-LASIK patient who has paid big money for no glasses, it is also devastating. A pharmacological cautery method would be a huge improvement in our surgery. Until then, minimization of cautery is advisable.

**Cataract**

We now know that one cannot treat glaucoma without causing the more rapid development of cataract. Whether the therapy is with eyedrops or surgery, surgical removal of cataract becomes at least 50% more likely with IOP-lowering. Better a treatable opacity than irreversible loss of retinal ganglion cells. But, patients must be aware that we have this issue to deal with. Where there is already
early or moderate cataract present, it is worth the discussion to consider a combined phakoemulsification – trabeculectomy for this setting.

Hypotony

Until the 1980’s, glaucoma surgeons lived in fear of removing the patch on day 1 after surgery – hoping not to see the shallow or flat anterior chamber. It would be present at least 10% of the time, and reformation with choroidal drainage was a relatively common procedure. Since the use of laser suturelysis or releasable sutures, we are more in control of the chamber and IOP. First, the method requires careful attention to the construction of the scleral flap and trabecular removal. The excision of tissue under the flap should not extend to the edge of the sclera, lest one have, in effect, produced an old-fashioned full-thickness procedure. Second, the sutures on the flap (10-0 nylon with buried knots) should be tight enough to hold the anterior chamber formed with a slow leak of fluid when the chamber is refilled. If no fluid exits, the sutures are too tight. If the chamber is flat within 30 seconds after reforming, tighter or more sutures are needed. Slipknots are very useful here to place the proper tension and to test drainage. They are then locked by putting a square knot over each. I have put 9 sutures on a scleral flap in a case of nanophthalmos with severe positive pressure from choroidal expansion.

Which is better: suturelysis or releasables? Among the six glaucoma specialists at Wilmer, two use predominately one method and the other four use the other. The advantages of laser suturelysis are:

- you can almost always do it
- flexible IOP control
- no need to remove them if the IOP is fine
- lower chance of infection than releaseables

I try not to suturelyse on post-op day 1, unless IOP is painfully or dangerously high. It often drops spontaneously by day 3-5, and both tenderness and subconjunctival blood are less at that time. As well, the conjunctival closure is more secure later. When the decision is made to cut, look at the chart and see which of the sutures you made tightest in the operating room (this should have been marked in the chart then). Or, cut the one closest to 12 o’clock to direct flow that way. If there is subconjunctival blood, use a krypton red laser, not one of green wavelength, to avoid the greater chance of energy uptake and formation of a hole.

Either the 4 mirror goniolens with handle (‘Zeiss’ or ‘Posner’ type) or the specially designed suturelysis lens can be used. The former holds the lid out of the way better with squeezers or baggy lids. Use the portion of the goniolens surface that typically contacts the cornea to press onto the bleb to flatten it (don’t shoot through the mirror). One must press quite firmly to push aqueous and capillary blood out of the way to see the 10-0. It should be melted with a 0.1 second, 50 micron spot at the lowest energy needed (about 400 milliwatt to start). If there is blood in the overlying area, it is quite possible to produce a hole. I have had to repair one such hole surgically (out of about 1,500 cases).

If one suture is cut and the bleb enlarges immediately (it often does as the lens is put in place), no further cutting is done that day. If there is no enlargement,
even with finger pressure through the upper lid next to the scleral flap, it is wise to regonioscope. There may be blood in the internal opening or an iris plug. The clot should be allowed to lyse over the next week before more suture cutting. The latter can be dealt with by YAG laser. If the IOP is still too high and the internal opening is unobstructed, a second or even the third suture may be lysed. However, this invites hypotony during the following week.

Tell each patient that sudden downshifts in IOP lead to some discomfort and blurring. Otherwise, you will get a call later that day. There is sometimes a dribble of blood from the wound internally into the chamber after lysis. The flap probably occludes capillaries that reopen when it moves. This has never been so significant that it hurt bleb function in my experience. If you wish, you can press through the lid over the flap like Hans Brinker to stop the bleeding (be prepared to hold your finger there for some minutes).

The downside risks of laser suturelysis are:

- Laser must be handy
- Blood under conjunctiva blocks the view
- Occasional uncooperative or nystagmoid patient will not hold still
- Should do tenonectomy to see better
- Can produce bleb leak with bad technique

Those interested in releasable technique can seek help in a number of other reports. I have found it useful in two cases in the last ten years. It is not possible to make some releasables tighter or looser (as one can with the suturelysis approach). Nor can they be left indefinitely, as they have on several occasions in our emergency room presented with bacterial ulcer tracks along them into the bleb area. To remove releasables without disturbing the scleral flap, the suture can be cut in the cornea with a laser, then pulled out from the cornea.

Hypotony

Despite use of tight scleral flap sutures and probably because of use of mitomycin in many cases, a dysfunctionally low IOP happens. It is a clinical problem in nearly 5% of my operations during the last five years. The differential diagnosis of low IOP after the immediate post-operative period should include:

- Overfiltration
- Inflammation (hyposecretion)
- Bleb leak
- Cyclodialysis
- Effect of fellow eye meds
- Systemic meds
- Retinal detachment
- Carotid insufficiency

So few have seen a cyclodialysis, that it may require consultation with a white-haired glaucoma expert to confirm it. The workup suggested below will help to be complete in reviewing the patient status in this situation:

- History: Are topical hypotensive medications used in the fellow eye that have a cross-over effect? Are systemic pills being taken that could lower IOP (beta-blockers, steroids)? Has there been trauma? Or, wrong eye delivery of glaucoma medication?
• **Slit Lamp:** Do Seidel test, look for flare and cells.
• **Gonioscopy:** look for cyclodialysis cleft.
• **Dilated retinal exam:** look for retinal holes (choroidals will probably be present on ultrasound regardless).
• **Neck exam:** is carotid pulse normal, is there a bruit, are carotid Doppler tests merited?

Do not forget that poor carotid flow on one side can lead to unilateral hypotony. At least one patient of ours completed a stroke prior to the completion of the workup to rule this out. Retinal holes serve as outflow channels; hence, the retinal specialist may be needed to differentiate between serous retinal elevation over choroidal detachment and a rhegmatogenous detachment causing hypotony.

Bleb leaks are frequently overdiagnosed. This derives from the failure to recognize that slow dilution of fluorescein over a thin bleb is not a leak, but is how blebs work. A true leak is a focal, brisk dark movement of fluid washing away the dye. A Seidel test should not be a contact sport. I abhor the use of fluorescein paper strips, which are guaranteed to remove valuable conjunctival epithelium when wiped across the bleb, making the problem worse. Standard fluorescent solutions used in tonometry are perfectly adequate to do the test (one does not need 2% solutions).

Bleb leaks sometimes heal spontaneously, in fact, about half of them do, if given the chance. However, the use of 'IOP-lowering' drops and antibiotics are to be avoided in this setting (despite being the present standard of care). Lowering IOP does nothing to help heal a leak. There are 6 ml of aqueous and vitreous fluid in the eye and decreasing aqueous flow with a beta blocker by 50% per minute is not going to prevent the eyelids from pumping fluid through a hole when there’s a huge reservoir of aqueous in there. Besides, don’t we want a higher, not a lower IOP? Antibiotics are now proven to make it MORE likely to have a later infection in this setting, not less. Late bleb infections were more common in those treated intermittently or chronically with antibiotics. They should be used when actual signs of infection are already present. With ‘preventive’ antibiotics, one is removing all the easy-to-kill Staphylococcus epidermidis and selecting for those fluoroquinolone-resistant Pseudomonas and Streptococcus viridans that will later invade and wipe out the eye. Leave the normal fauna alone. When used in a leak with no infection, the antibiotic itself and the preservative simply slows or even reverses the needed healing of the conjunctival epithelium over the hole by their toxic effects.

If the hole does not heal spontaneously, or if you are the type who buys hedge funds or believes in the tooth fairy, then put a large contact lens over it, put glue on it, or try to suture it closed. If you actually wish to fix it, do so surgically (which nearly always works), by removing the thin area completely and following the technique described above for bleb reduction. However, in the setting of low IOP, consider resuturing the scleral flap tightly and even placing tissue over it to reinforce its thickness. My favorite tissue to use is a wad of the patient’s own Tenons capsule, obtained by a fornix incision and spread out flat. It is sutured in place with 9-0 vicryl in interrupted sutures, over the area of the scleral flap. If this is going to obscure the view of the sutures (hence, preventing suturelysis), then releasables should be used. I have not had the need to use prepared pericardium or split-thickness eyebank sclera in a long time since using Tenons (which is also much cheaper and always available). I strongly suggest draining the fluid in the
suprachoroidal space in a hypotonous eye (two lower quadrant incisions); even when you cannot see the choroidal detachments clinically, they are often there, and will prevent rapid elevation of IOP.

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Simple strategies to improve the safety of trabeculectomy: 
The Moorfields Safer Surgery System

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Introduction

Glaucoma filtration is still one of the most effective methods to lower intraocular pressure to the levels in the low teens, associated with best preservation of vision.1 Despite the advent of other methods of glaucoma surgery, trabeculectomy is still the main operation performed around the world. The main reason for the advent of the other methods of filtration surgery has been side effects associated with trabeculectomy particularly hypotony associated symptoms and visual loss. The use of antimetabolites has increased the chance of achieving a lower intraocular pressure, but also an increased chance of developing complications. Important complications relating to hypotony can now be minimised by simple techniques. These techniques (Table 1) have considerably increased the safety of trabeculectomy and are described (Fig. 1). We have incorporated all of these into a single system of surgery we call the Moorfields Safer Surgery System.

Local anaesthetic technique

Sub-tenons anaesthesia separates tenons from the conjunctiva and episclera, allowing the conjunctival mobility to be checked when selecting the surgical site. Subconjunctival anaesthesia at the bleb site may be associated with a poorer outcome,2 possibly due to haemorrhage and tissue damage. Sub-tenons anaesthesia may also carry this risk, but did not have a significant affect on outcome in this large study, which may have been artefactual or real, due to the sub-tenons injection usually being given further from the operation site. Other forms of local anaesthesia, such as topical and intracameral anaesthesia, are being adopted for trabeculectomy, including topical lidocaine 2% sponges and unpreserved lidocaine

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Table 1: Complications of trabeculectomy and recent improvements in trabeculectomy technique that minimise these complications

- Rectus suture haemorrhage: Corneal traction suture
- Uncomfortable blebs: Position of the surgical site
- Poor early IOP control/hypotony: Scleral flap/sclerostomy design to produce diffuse aqueous flow and better intraocular pressure control
- Intraoperative hypotony/poor assessment of flow: Intraoperative maintenance of intraocular pressure – continuous infusion
- Cystic focal leaking blebs: Fornix based incision with better closure and wide area of antimetabolite application – diffuse non-cystic blebs
- Hypotony while attempting low target IOP: Adjustable sutures – controlled gradual reduction in IOP
- Conjunctival leak: Corneal-conjunctival closure techniques

![Diagram of changes in surgical technique that have improved the safety of trabeculectomy.](image)

Fig. 1. Changes in surgical technique that have improved the safety of trabeculectomy.

2% gel, which appears to be as good as conventional peribulbar and sub-tenons injection respectively. They achieved comparable pain control, no increase in stress by the surgeon and no increased complications. Intracameral unpreserved 1% lidocaine can be used to supplement topical anaesthesia.

**Corneal traction suture**

A corneal traction suture is more firmly fixed and therefore exerts a more consistent vector force (Fig. 2). We use 6/0 black silk 2 mm anterior to the limbus through mid-thickness cornea. In the UK National Study of Trabeculectomy, a corneal traction suture was associated with a better outcome than a superior
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Fig. 2. Corneal traction suture avoids subconjunctival haemorrhage – associated with better outcome.

rectus traction suture. A superior rectus suture may limit surgical access, put tension on the conjunctiva and cause scarring from haemorrhage or tissue damage.

Assessing and positioning eyelid position and the surgical site/bleb position to achieve a sub tarsal bleb

Eyelid position assessment is a critical component of surgical site assessment. The bleb is ideally in a position where it is totally under the upper lid, which provides additional protection from infection and exposure. Interpalpebral bleb extensions are associated with increased bleb leakage, predisposition to infection, subconjunctival haemorrhages and occasionally severe discomfort.

Technique of tenon’s dissection – plane dissection around and over superior rectus

Vasoconstrictor drops such as norepinephrine 0.05% help to minimize bleeding in the area of surgery. When dissecting over the superior rectus, the conjunctiva should be lifted to cut attachments, and not the muscle tendon, which minimizes bleeding. If there is preexisting scarring subconjunctival saline can help demarcate and open tissue planes.

Fornix based conjunctival flaps and large antimetabolite treatment area minimises cystic blebs

Bleb related complications have markedly reduced since we changed the way we applied antimetabolites to the conjunctiva. Based on clinical observation I postu-
lated that a larger area of treatment together with fornix based blebs would result in much more diffuse blebs, and I changed technique in 1996. We have shown that a cystic bleb morphology is more common with limbus based trabeculectomies in young patients undergoing mitomycin C enhanced trabeculectomy. Over several years, 90% of limbus based versus 29% of fornix based flaps evolved into cystic blebs. The degree of cystic change was also far more prominent with limbus based flaps, and this was reflected in a 20% rate of blebitis and infection as opposed to none in the fornix group (Fig. 3). Fornix based flaps provide a better surgical view and a diffuse antifibrotic application is easier to perform. They are less time consuming and the bleb is more diffuse, although it is possible to get this diffuse appearance with a large limbus based flap. The efficacy of fornix versus limbus based flaps in pressure reduction has not been shown to differ greatly.

In the past, the reason fornix based surgery is not more commonly performed was concern about the risk of early leakage and subsequent failure or infection in fornix based surgery. However, wound leak is not a risk factor for subsequent failure. Furthermore, careful closure of fornix based flaps can minimize leakage, especially using a new method we have designed of tight corneal conjunctival suturing (see below).

Scleral flap size – adequate to control intraocular pressure, cut and shaped to direct aqueous away from the limbus

Clinical observation suggests strongly that limbal aqueous drainage is associated with cystic blebs (e.g., full thickness sclerostomies and inadvertently anterior draining trabeculectomies) and more posteriorly draining aqueous (large flaps) is associated with thicker more diffuse blebs. To prevent anterior flow, we leave the sides of the flap intact 1 mm posterior to the limbus, to force aqueous backwards (Fig. 4). The thickness of the flap should be sufficient (half scleral thickness) to prevent dehiscence (and anterior drainage) and cheese wiring of sutures. The flap should be of adequate size to provide flow resistance (between the flap and base). These measures increase our ability to control intraocular pressure post operatively.
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Technique of antimetabolites application – polyvinyl alcohol sponges and large area of treatment

Non-fragmenting polyvinyl alcohol sponges are used rather than methylcellulose, to prevent retention beneath the conjunctiva\textsuperscript{12} (Fig. 5). Specially designed clamps (small conjunctival clamp No 2-686, www.duckworth-and-kent.com) may help, as they protect conjunctival edges so that that their healing is not inhibited post-operatively (Fig. 6). A large application of antifibrotic produces a more desirable thick and diffuse rather than thin and cystic appearance (Fig. 5) with a reduction in bleb related complications of blebitis and endophthalmitis.\textsuperscript{8} The dose of antifibrotic is varied by changing the concentration rather than time.\textsuperscript{13} A more detailed account on choice of antimetabolite is available elsewhere including potential newer anti-scarring techniques.\textsuperscript{7}

Fig. 4. Limited side cuts to prevent limbal aqueous drainage and cystic blebs.

Fig. 5. Corneal polyvinyl alcohol sponges lined up for insertion.

Fig. 6. Conjunctival clamp being used to hold conjuctival edge away from MMC sponges.
Maintaining intraoperative intraocular pressure and accurately gauging flow – anterior chamber infusion

Controlling the intraocular pressure is important both during and after surgery, as fluctuations increase the risk of supra-choroidal haemorrhage and large fluctuations of pressure can compromise residual optic nerve function, particularly in eyes with severe damage. Hypotony causes breakdown of the blood aqueous barrier with leakage of pro-fibrotic proteins into the eye. We use an anterior chamber infusion (Lewicky, Visitec) (Fig. 7) with a three-way tap to maintain a near constant pressure during surgery, and apply a known pressure when assessing the flap tension and resistance to aqueous flow. This infusion acts as a third hand and delivers the iris to the sclerostomy for the iridotomy without entering the eye (Fig. 8).

**Fig. 7.** Anterior segment infusion prevents hypotomy, presents iris and helps accurate tensioning of adjustable sutures.

**Fig. 8.** Iris presenting to sclerostomy due to infusion avoiding intraocular entry.

Small drainage channel using small scleral punch – improved control of fluid flow and intraocular pressure

A punch allows better control of the fistula creation and a smaller hole to be made. With antifibrotic agents it is critical that aqueous outflow is regulated to control early postoperative complications, and this is dependent primarily on scleral flap apposition and resistance. Our laboratory studies have shown that it requires a 40-50 µm diameter hole before there is any significant resistance at physiological aqueous flow rates, so we aim for a small sclerostomy to maximise flow control and use a 500 µm diameter punch (Fig. 9). Larger holes increase the chance of poor flap apposition and also post-operative astigmatism.
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Peripheral iridectomy – small with no intraocular entry

If an infusion is in place the fluid flow can be used to present the iris, avoiding intraocular manipulation. Entering the eye to manipulate the iris can cause damage to structures including the lens and zonules. With controlled flow only a small iridectomy is required.

Adjustable sutures with gradual lowering of intraocular pressures

Sutures are the major determinant of the intraocular pressure in the early phase after surgery. Laser suturelysis and other releasable sutures have been major advances which help control post-operative hypertony and hypotony. Sutures and the resultant scleral apposition provide the major resistance to flow across the flap in the early post-operative period prior to wound healing. Releasable sutures reduce short term complications associated with over drainage while improving the long term outcomes of bleb survival and pressure reduction. The lower flow rates do not appear to affect surgical outcome. However, sudden falls in intraocular pressure may still occur even after many several months in antimetabolite treated eyes, particularly with the use of mitomycin. We have developed an adjustable suture technique with special ultra smooth forceps (Khaw transconjunctival adjustable suture control forceps, No 2-502, www.duckworth-and-kent.com). The sutures are standard 10/0 (Alcon, Fort Worth Texas) and tied with four throws (Fig. 10). If mitomycin is used, two fixed side sutures are used for extra safety. The sutures in the flap can be manipulated transconjunctivally with the forceps that have special fine and smooth edges to prevent button-holing, with minimal discomfort under topical anaesthesia at the slit lamp in clinic (Figs. 11 and 12). The gradual decrease of knot tension allows flow to be slowly reduced to the required level, and can be adjusted up to several months later if mitomycin is used.
Fig. 10. Tying technique for Khaw adjustable sutures.

Fig. 11. Khaw adjustable suture forceps.
Conjunctival closure – corneal anchoring sutures

We use an anchoring corneal suture technique (corneal groove closure) which we designed to seal the conjunctiva under tension without the commonly used mattress sutures (Fig. 13). Half thickness clear cornea grooves are preplaced 2 mm from the limbus, with 10/0 nylon passed through the groove and conjunctiva, with the knots buried in the cornea. These sutures are comfortable and there is no need to remove them.

Fig. 12. Transconjunctival adjustment of sutures.

Fig. 13. Technique for coneal anchoring sutures for fornix based conjunctival incision.
Early post-operative identification of blebs at high risk of failure – bleb scoring including Moorfields bleb scoring system

Prospective assessments of bleb morphology may be useful in predicting failure and complications in the future and modify the postoperative management of the bleb. Several bleb classifications have been proposed. The Moorfields bleb classification which we use is easily ratified and the vascular scoring in particular is correlated with long term failure, suggesting situations where post operative 5-fluorouracil is required. The system is readily available on www.blebs.net.

Post-operative treatment – close monitoring, steroids and antiscarring agents

Intensive postoperative treatment in primary trabeculectomies improves intraocular pressure and acuity. Increased inflammation and scarring in the early postoperative period is associated with a poorer outcome, and the management is labour intensive and may involve suture adjustment, anti-metabolite injection or needling. Topical steroids are usually applied two-hourly and then tapered over three months, and this has been shown to improve the prognosis of glaucoma surgery.

Systemic steroids and immunosuppressants can be used in particular high risk groups, but are not routine and can have serious side effects. There is at present no evidence that systemic steroids improve the prognosis of trabeculectomy although experimental studies with new immunomodulatory agents have been promising. Post-operative injections of 5-fluorouracil can be used to improve the post operative prognosis (FFSS) and they can be combined with viscoelastics to improve delivery and minimise complications (Fig. 14). In the future, injections of antiscarring agents at regular intervals may also improve the long term prognosis of surgery.

Fig. 14. Viscoelastic wall to minimise side effects of subconjunctival 5-fluorouracil.
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Conclusion

These advances in trabeculectomy technique have considerably improved the safety and efficacy of trabeculectomy. Most of these changes are simple and can be adopted and adapted immediately for use in surgery. The key to most of these improvements lies in control of how and where aqueous flows and the healing response. Future advances in cell and molecular biology, nanotechnology, innovative surgical techniques and biological materials has the aim to result in the ideal surgery that is scar less, with no complications and pressures in the low teens which is associated with minimal or ideally no glaucoma progression.

Further material (Videos)

Videos of these techniques can be downloaded from http://www./ucl.ac.uk/ioo/research/khawlibrary.htm. Details of the instruments are available on http://www./duckworth-and-kent.com. None of the authors have any financial interest in the products or techniques in this article including the surgical instruments.

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Round Table

Building a better drainage system – perfecting the trabeculectomy

Moderator: Katherine Loftfield, MD
Panel: Chris A. Johnson, PhD
Eve Higginbotham, MD
Paul Palmberg, MD, PhD
Harry Quigley, MD
Kuldhev Singh, MD
Peng Khaw, MD, PhD

Dr Quigley: Peng, do the conjunctival closure sutures come loose and do you ever have to remove them at the slit lamp?

Dr Khaw: If you pass the cornea sutures though the slits and tie them tightly, they do not come loose and they do not need to be removed. You made a comment concerning a limbus versus fornix based conjunctival flap. This is quite important. How many people here do limbus-based? Okay. How many people do fornix-based? So, it’s quite a mixture.

Dr Singh: I think clearly the big point you hit upon is that it is better to have a low, diffuse bleb than to have a focal cystic bleb. I think with certain limbus-based techniques, you do get focal cystic blebs. These cystic blebs can be avoided by applying the antifibrotic with a lower dosage over a broader area and by making your incision at least 10 mm back from the limbus. I think you get the same types of blebs that you are showing with the fornix-based technique.

Dr Higginbotham: I agree with Kuldev that if you apply the antifibrotic agent over a diffuse area you can avoid local cystic blebs. We learned from the 5-fluorouracil filtering study that if you have an early leak you’re going to have a higher risk of failure long term, and that’s from one of the clinical trials. I am concerned about having those leaks early on with the fornix-based conjunctival flaps.

Dr Quigley: I have been doing both. It depends very much on what the conjunctiva is like, especially if you are re-operating on somebody. Suppose the patient had a large incision cataract operation ten years ago and now you need to do a filter on them. The fornix-based flap is a lot easier to pick up than to dissect your
way from the back end, where everything is all kind of stuck down. Sometimes you will do a limbus flap and come forward toward the limbus and all of a sudden everything just comes off and now you have a floating bridge of conjunctiva and you essentially have both, conjunctiva fornix and limbus flap to close.

Dr Palmberg: It may be possible to get these kinds of blebs with limbus-based flaps, but I think it certainly easier to get them with a fornix-based flap. If you ever have to do some more surgery like a Baerveldt, it is awfully nice for the only previous incisions to be located at the limbus. I think you get a whole lot more ptosis if you pull the eye down to get back 10 mm. When dissecting a fornix-based flap you are not pulling on the eye a lot. I think I have a lot less ptosis than I used to get.

Dr Khaw: I do agree. I think with the limbus-based incision it is possible to get the diffuse bleb. One of the reasons that we do less of that is because we don’t get leaks at the limbus. The exposure is a lot better with a fornix base, and if you are doing a re-op, it is much easier to do a fornix-based incision. Either way, you need to keep a broad diffusion area.

Dr Loftfield: This question concerns people who have functioning preexisting trabeculectomies who need to go to cataract surgery. What is the bleb failure, and do you have any pearls or tricks to try to minimize bleb failure?

Dr Quigley: You have an existing bleb and now you are going to do a cataract. You are going to perform clear cornea cataract surgery. I don’t have a formal read on our present rate but most of the trabs are still working.

Dr Higginbotham: If the bleb is thin, you might want to overfill the anterior chamber so the bleb is filled with Healon or some viscoelastic. Postoperatively, you may need to touch up the bleb by giving the patient 5-FU injections if you start seeing a little bit of contraction. I think most importantly, watch the bleb postoperatively to make sure that it’s not responding negatively to the insult of having undergone a phaco.

As in Harry’s case, I have not formally looked at my series, and I generally will send the patient back to the general ophthalmologist who does the cataract. I will ask them to have me see the patient postoperatively so I can actually look at the bleb.

Dr Quigley: We should distinguish between the patient who has had a trabeculectomy and now they are back on let’s say Alphagan and Xalatan and their pressure is at target, but they are on two drugs and now they need cataract surgery, and the patient who has a pressure of ten on no meds at all with a relatively thin bleb and now they need cataract surgery. In the case of the patient who is already back on two kinds of medicine, I do a second trabeculectomy when the cataract is done. If the patient is on no medicine at all, then I would perform the cataract surgery alone.

Dr Loftfield: And do you do a complete, separate trabeculectomy, or do you try to revise it?
Dr Quigley: I perform a separate trabeculectomy – because you will kick yourself up one side and down the other when the pressure is 42 on the second postoperative day and you were there and you could have done something.

Dr Singh: I agree with everything that has been said. One thing I have thought about which I haven’t tried yet... the reason these blebs will fail postoperatively sometimes, I believe, is because you run a lot of fluid through the bleb when you are doing your surgery. If you do a short operation and there is minimal inflammation, I think they do better than if it’s a long operation, a lot of inflammation. One thing I have thought about is using Healon 5 to compartmentalize the area where the trabeculectomy fistula is so that you’re not running fluid through the bleb during the time of surgery. Then you remove it at the end of the case. Probably the next time I do a straight cataract on someone with trabeculectomy I am going to try that.

Dr Palmberg: I think the things Harry said about which cases you are going to do something more on I would agree with completely. Sometimes the bleb doesn’t look too bad and at the end of the phaco you can put a cyclodialysis spatula in and do a little work inside on up through the fistula and revise it a little bit the way Dick Simmons talked about. I think that can be kind of a bridge between the one you’re going to really re-do and the one where you don’t have to do anything.

Dr Khaw: I agree with everything everybody says. I watch the patients carefully and I think, although there is no good evidence in the literature, if the bleb is beginning to fail then consider a course of subconjunctival 5-fluorouracil.

Dr Loftfield: The next question is regarding your postoperative regiment of steroids. How long and how hard you are hitting them with your postop steroids after trabeculectomy.

Dr Higginbotham: I continue steroids going for at least eight weeks. I think one of the things I have noticed with the residents, they tend to want to stop the steroids sooner just because that is what they do with cataract surgery. Steroids may be administer for at least eight weeks up to four times a day and then out to three months they still might be one to two times a day, but certainly after three months they are not.

Dr Quigley: It’s every two hours for a week; if they are still red or inflamed that goes on for a second week. If they are not, it goes to four times a day. The average is between six and eight weeks of total steroid, tapering 4-3-2-1 and out over a week. We have a piece of paper we give them for what the schedule should be and it has the dates on when you go from four times a day to three times a day. Perhaps I am a little different from the rest of the panel in that I don’t use any antibiotics whatever and I don’t use cycloplegics postoperatively, because they are useless except for keeping posterior synechiae from forming. I dilate the patient on each postoperative visit to keep the pupil moving.

Dr Singh: I use steroids a little bit longer, minimum three months. I start every two hours for one to two weeks, then every three hours for usually one to two
weeks, then four times a day and taper it one drop every two weeks once a day and then usually stop the steroids about three months. I have some people on steroids for six months after surgery. As far as cycloplegics, I agree with Harry, I don’t think most of these patients need them. I use atropine intraoperatively at the end of the case and then most of the time if the chamber is deep, pressure is decent, I usually don’t use it. But I do use antibiotics, I agree with Harry, there is really no evidence that shows they are beneficial. It is just kind of the standard of care in our community. One other point about postoperative steroids, in the previous question about the patient that has a filter where you do a cataract, I treat those patients postoperatively with steroids the same way I do with a trabeculectomy. I leave them on steroids for at least a couple of months, generally three months, and not taper like I normally would after a straight cataract.

Dr Khaw: We administer steroids for three months, two hourly for one to two weeks and then taper down to four times a day rapidly. We will keep that going until pretty well the end of the three months. I think we have all seen patients in whom steroids had been stopped either accidentally or too quickly and then very rapidly the bleb fails. We do not use cycloplegics. Cycloplegics are for pain. They don’t really get pain if you control them well. Posterior synechiae – I don’t think I have seen that for a long time now. The other thing about cycloplegic is it blurs their vision, so they get very annoyed at you.

Dr Palmberg: I use a regiment of steroids similar to what Kuldev described, except that if the patient has rather red eyes from being on multiple drugs, I also try to use preservative-free methylprednisolone. If the patient is pseudophakic either because we did a combined or they are already pseudophakic, I would never stop steroids. I keep the patient on steroids twice a day for life. Because otherwise blebs in these eyes tend to get smaller and you are not worried about steroid glaucoma, you are not worried anymore about causing cataract. There is no reason not to use it. There is some evidence that you keep the enzymes in the tissue that tend to eat holes in blebs suppressed by giving steroid, and you are less likely to get an infection if the bleb doesn’t shrink and get smaller and become a focal cystic bleb.

Dr Higginbotham: I wanted to comment on steroid-induced increased intraocular pressure. Jacob Wilensky, who is also from New Orleans and went to Ben Franklin High School, wrote a case report where he noted that a patient post trabeculectomy had an increase in pressure. That is something you have to think about if you have cut all the stitches and the pressure is up, sclerostomy is open, that you might want to consider Vexol. I might actually switch those patients to Vexol 1% if I still need that intensity. If I don’t really need the intensity, but just need a little steroid because of a lot of hyperemia around the bleb, then I might use FML.

Dr Loftfield: So you do believe that some bleb patients can still have a steroid-induced glaucoma?

Dr Higginbotham: Yes, definitely, as Jacob described.

Dr Quigley: The most common thing that happens when somebody postoperatively has a high pressure after trabeculectomy is you will see a bleb that looks
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high and dome-shaped and opalescent and we wrote a paper about that called ‘The High Dome Bleb Phase after Surgery’. The best thing to do, which you would do anyway because the pressure is high, is to put the patient back on something that lowers the high pressure. What is happening is that the bleb wall, which is like a sponge, gets compressed. The bleb goes into a bad cycle of increasing compression, decreased water going through it, increasing compression, even less water going through it, pretty soon you have a high, tense, relatively thick looking bleb. If you lower the eye pressure chronically, the bleb wall will go back down to a spongy area with fluid going through it again, and you will ultimately be able to stop the pressure lowering drops in many of those patients. A paper was written by Doug Scott in *Ophthalmology* in about 1890 or so, if you want to read about that phase. I don’t believe it is actually a steroid response as much as it is a responsiveness of the bleb wall at a particular time after surgery, and it’s salvageable.

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**Dr Loftfield:** Along the same line as steroids, the Pred Forte and the prednisolone acetate we were talking about, someone has a question about using Decadron. Do they feel that you could leave them on maybe Decadron drops once a day forever as opposed to Pred Forte or prednisolone acetate? Does anyone have any experience with switching them to Decadron?

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**Dr Palmberg:** Sometimes I have had patients who are uncomfortable with prednisolone acetate. I frequently go to prednisolone phosphate, which is clear and doesn’t have a residue with mucus. They are more comfortable. I have tried Decadron. I can’t see any reason not to use it. It probably raises pressure more, but if you’ve already got a bleb it doesn’t matter.

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**Dr Khaw:** I use prednisolone forte 1% because in the studies that have been done it’s the strongest anti-inflammatory. If they are having surface problems, then I will change them to Dexamethasone preservative free. I think the comment about the pressure rise is true.

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**Audience:** I am not sure about in Europe, but in the United States Merck stopped making Decadron drops and the ointment. Does anybody have any experience injecting Kenalog intravitreally following trabeculectomy for the long term steroid?

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**Dr Singh:** That’s a great question. Dr Gills, do you want to comment on that? Let’s get someone who knows what they are talking about.

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**Dr Gills:** I have done a few, but I haven’t done enough to really make an educated judgment that it worked beautifully. I haven’t had enough experience to go out and say, go do it. Wait until I do a few more before I tell you. But it worked great on the ones I have done. I just haven’t had that much experience.

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**Dr Singh:** Many of us on the glaucoma net have been commenting that some of the most beautiful filters we see are in people who had steroid induced glaucoma after an intravitreal steroid injection. You don’t have to worry about them taking their prednisolone acetate afterwards. I think it is a viable modality. I think that
Decadron ointment leaving the marketplace was a negative. I used it routinely at bedtime.

Dr Quigley: You’re stuck with Pred-G ointment which has an antibiotic, and I refuse on those grounds. Jim, probably what we ought to do is a study in which we have high risk for failure trabeculectomy patients who get intravitreal versus not. Because the success rate of trabeculectomy is high enough that seeing whether there is an additional beneficial effect is going to be very difficult in routine trabeculectomy. Probably the study that should get done is in previously operated eyes, pseudophakic eyes where you are going to do a trabeculectomy anyway where the success rate might only be 60% or 50% or something, then giving it a shot there.

Dr Palmberg: One pearl. If you’re doing a Baerveldt on somebody who has had the vitreous taken out, particularly with these uveitis patients where this has been done, putting in the triamcinolone in the vitreous cavity at the end of the vitrectomy and before we put our tube in has really made an amazing difference and you didn’t need a randomized trial, because I used to see fibrin in these eyes, JRA kind of eyes, and in that situation I think it is strongly indicated to do it. But you’re right, the question about other situations, especially trabs, I have no information.

Dr Loftfield: The next question regards doing filtration surgery in a patient who is already pseudophakic, presumably with good, healthy conjunctiva that you have to work with. What is your surgery of choice – some kind of a seton or tube, or is it a trabeculectomy. We will start on this side with Dr Palmberg.

Dr Palmberg: While we are doing a randomized study in those patients, I suspect we are going to find high success with either one. There maybe an advantage for the Mito-filter if you really think the patient needs 10 or 12 for some reason. You are probably going to get 13 or 14 with a Baerveldt. On the other hand, if they have posterior or anterior blepharitis that you can’t get under control, then I sure would want to place a tube. If there is conjunctival scarring for some reason that you can’t move the conjunctiva easily with a Q-tip, that would be another reason to use a tube. Otherwise, I think either a trab or tube works quite well.

Dr Khaw: I agree with Paul. Particularly if you are using mito with either of them. With trabeculectomy, I obtain tighter control of IOP and can better titrate the pressure down to a target pressure. With tubes, I think I get a slightly higher success rate if they have very high risk for failure. If I particularly want the low target pressure and I want to titrate it down to the right pressure, I will use a trabeculectomy with mito.

Dr Higginbotham: I think with rare exception, every patient I think deserves at least one chance at a trab, so I will try a trab with Mitomycin-C in that instance. My concern about putting a seton in first, you can’t do the opposite. You can always do a seton after a trab, but you really aren’t going to expect to get any real success if you try a trab after a seton.
Dr Loftfield: Dr Khaw, is there a special forceps that you are using for suture adjustment post trab, and exactly how do you do this?

Dr Khaw: Yes, there is a special suture. It’s made by Duckworth and Kent. I have no financial interest. It is a specially machined edge that is smooth so that it doesn’t cut the conjunctiva. I have been doing this for three and half years or more. Unfortunately, the name of the instrument is the Khaw adjustable suture forceps. And how do you use it. Well, initially you can either just gently push down on the adjustable suture so you get bowing of the suture and loosens a little bit, or you can actually grab the suture through the conjunctiva and move it sideways and that will loosen the suture but not pull it out. The pressure will drop a few millimeters, but not 10 or 20 mmHg.

Audience: We want to push for these posterior diffuse blebs and some of these patients are going to develop a ring of steel and form these avascular blebs and leaks. What is the time course for a ring of steel and how do you manage it?

Dr Khaw: I think everybody has their method of dealing with the ring of steel. My method is needling. I’m sure probably everybody does the same. We will do a posterior needling, several needlings, so that you release the fluid posteriorly. I then use subconjunctival 5-fluorouracil. I mix it with Healon GV because then you get a depo slow release 5-FU as opposed to just stuff that runs into the tear film. That has been very useful as well and that is a good strategy.

Dr Quigley: You think everybody knows you are talking about the slit lamp, is it something you’re just doing in the office?

Dr Khaw: You can do it in the office. I have done it both in the office and in the OR; for a variety of reasons, we now tend to do it much more in the OR. But you can actually do it at the slit lamp.

Dr Quigley: This is happening within your two to three week postoperative period?

Dr Khaw: I was just saying this to Paul, we don’t get nearly as many encapsulated blebs since we are doing the wide area fornix-based. It is much less common to get an encapsulated bleb.

Dr Quigley: You can wind up trying to needle a bleb many months or years after doing the surgery, because the filter can fail at two years or three years. In my experience, it is not a technique that has a great success rate. It is something I say to the patient, “you know, we are scheduling you for a re-operation, but before we do that, how about we try this needling thing just on the chance that it is going to work.” That is called managing expectation.
Questions and Answers

Presiding Physician: Jill Koury, MD
Panel: Harry Quigley, MD
         Eve Higginbotham, MD
         Paul Palmberg, MD, PhD
         Richard Mackool, MD
         Peng Khaw, MD, PhD

Dr Koury: Is there a study that compares the relationship between age and cup to disc ratio?

Dr Quigley: If you look at population data where the cup to disc ratio is rated against age, the cup to disc ratio gets slightly larger in cross-sectional data, and if you interpret that as being appropriate for an individual who would age over a 40 year span, then you lose a few ganglion cells every year. The best estimate is that you and I lose between 20 and 25% of our ganglion cells during our lifetime.

Dr Koury: Do you use Mitomycin for all tubes or just tubes in children?

Dr Khaw: I use Mitomycin for all tubes, because I need to get a low target pressure and I use staged procedures to get the pressure right down to the low teens – all tubes.

Dr Koury: Dr Khaw, have you done comparisons between 5FU and Mitomycin in your institution? What are the results?

Dr Khaw: We haven’t done a formal randomized study, but there are two randomized studies and interestingly the randomized studies are finding it very hard to show the difference between Mitomycin and 5FU. The proviso of that statement is that the attendings were allowed to intervene postoperatively and therefore, inevitably I am sure what they did was by intervening, needling, and adjusting sutures, they were probably able to make the two groups closer together. Certainly, from the randomized point of view, it is very hard to show a difference between Mitomycin-C and 5-FU. Clinically, Mitomycin gives you a lower pressure, but you do pay a price, because it does lead to more problems with hypotony.

Dr Palmberg: I did consecutive series. It is not quite the same thing, but they looked identical (this was with five injections of 5-fluorouracil in the first two weeks, not the sponge) and we found an average pressure of 10 after 10 to 11 years with Mitomycin or 5-FU. It made no difference in pressure control or failure, and we didn’t have
that much difference in complications either when we used five injections of 5-FU compared to Mitomycin – a little bit more leaks, a little more infection with the Mitomycin, but not any more hypotony. I think we got more attuned to thinking about hypotony and what to do about it as years went on, and that gave the impression that Mitomycin was causing hypotony. 5-FU can certain do it too, if you don’t have proper scleral resistance.

Dr Quigley: We have six glaucoma specialists at Wilmer and our fellow is about to do a little exogesis in which she has watched all of us operate, and she is going to give us a little talk and say that you guys aren’t doing the same operation. There is not one of you that is doing what the other one is. When you begin talking about comparing across clinical trials trabeculectomy methodology, as Peng said, there is a lot of stuff that goes on postoperatively with suture-lysis or releasables, with how you manage the steroid, with what you are doing with needling and other stuff, that is very hard to control in one series versus another; it is even very hard to control within one series. This is one variable among a very large number of variables in glaucoma surgery. In addition, the outcome measures are not necessarily the same in studies as you compare them. I certainly agree with what Peng says – you pay a price for Mitomycin, but it’s worth it a lot of the time.

Dr Palmberg: I think how you apply these drugs makes a great deal of difference. When you used 5-FU, what was that sponge like? Did it force fluid into the tissue, or was it just a thin thing laid there with the conjunctiva on top? It is quite confusing to me about 5-FU with sponges. There are four randomized trials now – two in Latin America that showed no benefit. You didn’t show any difference in pressure, and yet the one Kuldev will tell us about perhaps with 5-FU versus Mitomycin, the average pressure was 10 and 11, not 13. In some studies it looks like 5-FU and a sponge is very effective and in others it doesn’t. I wonder if it’s how 5-FU is applied. We know it makes a tremendous difference in Mitomycin how the sponge is put in, whether it is a full sponge shoved in or it’s a thin sponge and you just lay tissue on top, how much does it penetrate, time, concentration. The method of using Mitomycin or 5-FU, as you say, what one person does could be quite different from what other people are doing, and the results will reflect the difference.

Dr Koury: One related question to Dr Khaw, do you now use 5-FU in post-op care, or only at surgery?

Dr Khaw: I do use 5-FU in post-op care. The evidence for using post-op injections of Mitomycin or 5-FU, is not fantastic. A Cochran analysis of the literature suggests that if you give less than three injections of 5-FU, you can’t find a trend that the post-op injections make much difference in trabeculectomy outcome. Having said that, I do use post-op 5-FU injections. If I feel the bleb is failing and it showing the signs, the pressure is rising or there is injection in the eye, then I use subconjunctival injections of 5-fluorouracil.

Dr Quigley: And sacrificing a goat helps.

Dr Koury: What patient characteristics would make you more likely to choose
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5-FU instead of Mitomycin during primary trabeculectomy, *i.e.*, age, specific risk factors, and so on?

**Dr Khaw:** I obviously see very high risk patients, so generally I use much more Mitomycin than 5-fluorouracil. I think Paul may disagree on this, but certainly in general use out there if you have an elderly patient, which accounts for a great many of our patients, who have few risk factors, who are not advanced, then 5-fluorouracil is appropriate for a lot of our patients.

**Dr Koury:** Dr Khaw, one follow-up question, what kind of sponges were used for the 5-FU sponge study?

**Dr Khaw:** The sponges that were used in the 5-FU study were methylcellulose sponges. Having said that, we now all use polyvinyl alcohol sponges. The reason for that is that we and others looked at this and you just don't get fragmentation with the polyvinyl alcohol sponges. I am sure all of you have experience with using the other sponges; you get all sorts of bits all over the place. So we now use polyvinyl alcohol sponges.

**Dr Palmberg:** For Mitomycin, I just cut off the side of a Weck-Cel sponge and it makes a piece about 6 x 4 mm and very thin and we have gotten quite good results and thank goodness, only one late leak and so far no infections in five years. That was an incredible change from six percent. Before putting any fluid on it we cut the sponge, then we apply the antimetabolite.

**Dr Higginbotham:** I certainly would consider using topical 5-FU in a patient that is a high myope and a patient that is younger than 45 years old, just because of the fact that there is a greater likelihood of having hypotony occur following the use of Mitomycin in those instances.

**Dr Koury:** There are very positive reports from India of a large series of congenital glaucoma cases in which combined trabeculectomy plus trabeculotomies were done. Dr Khaw, do you combine these two procedures, and would you use antimetabolites in those cases?

**Dr Khaw:** This is comes from Anil K. Mandal’s very large series. He is a fantastic surgeon and he has carried out really the world’s biggest series of these trabeculotomies/trabeculectomies. I have done trabeculectomy/trabeculotomy, and I find them tricky. The way we do trabeculectomy now relies on very tight control of the scleral flap and how fluid flows. The problem is when you do a trabeculotomy at the same time you do lose that control. So personally I do not perform these combined procedures. But I have to say his results are truly remarkable. I think if you are good at it and you get good results, then I would say continue it.

**Dr Koury:** Dr Higginbotham, how can we join with our optometric colleagues for more effective outreach to the underserved?

**Dr Higginbotham:** That’s an interesting question. In my spare time I chair the Planning Committee for the National Eye Health Education Program, which is the educa-
tional arm for the National Eye Institute, to coordinate the activities of about seventy organizations that are out there doing the work of increasing awareness about eye disease. The Academy of Ophthalmology is one of the partners as well as the American Academy of Optometry. I invite all of you to become more involved. Because yes, they are more engaged and whatever you can do in your local communities to be more involved is the first step. Certainly, people that are out there doing the glaucoma screenings or vision screenings are invariably optometrists, but there is no reason why we can’t see more ophthalmologists.

Dr Koury: Thank you Dr Higginbotham. Dr Mackool, with bimanual phaco, is there an increase in wound burn since the phaco tip has no sleeve?

Dr Mackool: Well, it depends on whom you talk to. The real truth is, yes, there have been some wound burns out there. Nobody knows the incidence. I think the wound burns occurred with a 1.1 mm incision. But not when using 1.5 mm incisions, because they leaked and the wound burn issue went away.

Dr Koury: Dr Khaw, how do you manage Sturge-Weber glaucoma in very young children? What is your procedure of choice?

Dr Khaw: Obviously, Sturge-Weber is one of the conditions which everybody fears greatly. Almost all these children who have glaucoma have a choroidal hemangioma, which obviously is a risk when you are doing penetrating surgery. One of the fellows has evaluated our experience with fifty-five patients with Sturge-Weber glaucoma. Initially, we either perform an angle surgery or a trabeculectomy. Angle surgery works well for about a year and then it begins to fail. So angle surgery is a good short-term procedure if you feel that drainage surgery isn’t good. We have been comparing two other groups – one who had beta radiation, which was our standard, and the new lot who have had Mitomycin. If you consider an IOP of less than 21 a success, then Mitomycin trabeculectomy provides an 85% success rate over two years, and if you use beta radiation, the success rate is only about 70%. So our standard treatment, if there is no contraindication, is a Mitomycin trabeculectomy with the large surface area treatment.

Dr Quigley: I’d agree with trabeculectomy. I think your biggest fear is not bleeding of the episcleral hemangioma because while it looks like heck as you start the surgery, it actually doesn’t bleed that much more than the episclera normally bleeds. Your real concern is choroidal expansion. Because with a low intraocular pressure, the choroid tends to expand and you get a very large choroidal so-called detachment. That is now going to be the wrong term for it, but that’s okay. They can maintain this choroidal detachment for an extended period of time, which sounds good for the pressure but is bad for the lens.

Dr Palmberg: We have gone to using Baerveldts in all of these kids and getting away from filtering surgery partly because with HMO’s and managed care in our area it was very difficult to follow blebs in children. They went from pediatrician to pediatrician and they all decided they could treat that red eye when it occurred. It is difficult to examine these kids. Certainly you can’t adjust your filter by lasering stitches or something afterwards, so we have had very good results. Also, you don’t
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have to decompress the eye at the time of surgery and get those retinal effusions or whatever you want to think of them in those cases.

Dr George Ellis: I have a question about pediatric glaucoma. I know that there is a wealth of experience up here, although Dr Khaw did give the lecture on congenital glaucoma. Maybe the other glaucomologists could jump in on this as well. What is your operation of choice for an African American baby born with cloudy corneas and diameters of 12 and 13 mm with intraocular pressures of 30 and 40 mmHg on Timoptic and Diamox at 10 mg/kg every six hours? What would be your initial procedure that you would want to do and how quickly would you do it and why?

Dr Quigley: George, how did you measure the pressure? What was the anesthesia and what was the machine you used?

Dr Ellis: Tono-Pen under Ketamine anesthesia.

Dr Higginbotham: Except for the buphthalmos, that describes a patient I recently had. We caught this patient just at three weeks of age. So the ocular enlargement hadn’t started yet. My choice at that moment was trabeculectomy/trabeculotomy. I always like to supplement it, particularly in those patients that do present with cloudy corneas and I am concerned about the long term issues. Invariably, the trabeculectomy doesn’t really give me a cystic bleb in this age group anyway, but I guess it gives me a little bit more comfort in case I am not happy with cannulating Schlemm’s canal on both sides. I generally would use trabeculectomy/trabeculotomy with Mitomycin C.

Dr Koury: Eve, when you do your trabeculotomy, do you use a trabeculotome or do you use a suture?

Dr Higginbotham: I use a trabeculotome.

Dr Quigley: Bilateral trabeculotomy at one sitting, and I think you give the angle surgery a chance. Success rate in that particular setting is probably fifty percent. You maybe going back to do another trabeculectomy later. Don’t center the thing right straight up at 12 o’clock, because it will interfere with the later trabeculectomy.

Dr Ellis: And how long do you give that angle surgery to work?

Dr Quigley: If it isn’t down at six weeks you are going to have to move. We would typically do an EUA early at a month to six weeks and see what the pressure has done. If the cornea clears, you already know what is going on.

Dr Ellis: If the cornea doesn’t clear, in which amblyopia is a big issue here, then you’d have to go in sooner.

Dr Palmberg: We really like to do Mary Lynch’s operation using Prolene suture passed 360 degrees around and get all the angle surgery done at once. We do this temporally so that you are doing almost nothing to the superior conjunctiva. Our
usual second choice would be to put in an inferonasal Baerveldt, which also saves
superior conjunctiva or it could be put superotemporally.

Dr Khaw: We have had about five of these children over the last two years and
we have used goniotomy in all of them and they seem to do okay. All of those five
have pretty good pressures. We have had to strip their corneas with alcohol at the
time, but that grows back after about three or four days. The advantage I have of
using goniotomy is that you effectively have a virgin eye when it comes to doing
any secondary procedure and you haven’t altered the conjunctiva.

Dr Ellis: The reason I asked is because the literature says that a child born with
buphthalmos, cloudy corneas and a high intraocular pressure signifies that the anatomy
of Schlemm’s canal is not well formed. I was curious as to why would a goniotomy
work or why would trabeculotomy work.

Dr Khaw: I didn’t quite catch the age of presentation. The ones I am talking about
are the ones who usually present at two or three months. Your child presented at
birth?

Dr Ellis: Yes, the neonatologist noted in the ICU on day one and ophthalmologist
examined on day two and transferred him to us on day three.

Dr Quigley: I am unfamiliar with any actual histology that shows that those children
are different from kids who presented three months or six months or one year. I
think you are having surgeons guessing what they think is true of Schlemm’s canal
when they went in to operate. We actually don’t put the probe in Schlemm’s canal
anyway; we put it in the scleral sulcus. So whether there is a Schlemm’s canal or
not may or may not even be relevant.

Dr Palmberg: That is a very important point. If you get in there and can’t find
Schlemm’s canal, just do what would be I guess a cyclodialysis kind of incision…
Doug Anderson taught me to do this if I ran into that kind of case… and the corneas
cleared and they did well. I do not understand the anatomy of what we fixed.

Dr Quigley: The trabeculotome probe is about three to four times larger than
Schlemm’s canal. And Schlemm’s canal is discontinuous in most adults, it is prob-
ably discontinuous in children. So we are making false passages a lot of the time
probably.
Questions and Answers

Presiding Physician: Ramesh Ayyala, MD
Panel: Richard Mackool, MD
        Paul Palmberg, MD, PhD

Dr Ayyala: Dr Mackool, I have questions for you from the audience. Why do you think if endocyclo-photocoagulation (ECP) is such an effective procedure there are no peer review publications on the procedure thus far? We keep hearing about ECP as something that is a viable option. Because it shuts down the aqueous production, do you think it is good for an eye?

Dr Mackool: I can only answer for myself. We have tried to submit our data and they keep asking for more and more statistical analysis, and I think that we cataract surgeons frankly just say, you know, it’s not our bailiwick anyway. We just do them, follow the results, and if clinically they are good… it’s just the truth. I’m not a glaucoma guy who is really interested in proving all kinds of glaucoma stuff. I am interested in satisfying my glaucoma referral specialists that it works, and they seem to be happy with it. I don’t know what other data has been submitted by various sub-specialists. I think one factor that has inhibited its acceptance is the fact that it is a ciliary destructive procedure. The last thing a cataract surgeon wants to start doing is ciliary destructive procedures. I don’t know what its penetration into the world of glaucoma surgeons has been, but if it has been relatively low, I think it is because of the abysmal history of ciliary destructive procedures in general. At the very worst, you do the case and it doesn’t work. That is the very worst thing I have ever seen. I have never seen anything worse than that – temporary iritis. I perform ECP instead of one eye trabeculectomies. I get patients sent to me who are out of control and it is their only eye and I tell them, “Look, the glaucoma guy can do a trabeculectomy if my ECP doesn’t work.” I don’t want to do one eye trabs. I don’t want to do any trabs, to tell you the truth, but I certainly don’t want to do one eye trabs. So far, they all go for their ECP and very few of them have actually needed trabeculectomy. I have no financial interest in the company.

Dr Palmberg: Which are the cases that you do and which are the cases that you wouldn’t do. You have mentioned controlled people where you are reducing medication, which sounds like a pretty safe bet. What about somebody whose pressure is 30 on three meds and you think they need twelve. Would you still do that as a combined?

Dr Mackool: In the case that you just mentioned, to get the pressure down to 12 in that eye probably isn’t going to happen. You are more likely to get four or five
points of lowering and get them off of a medication as your best case result. For the case you described, the uncontrolled case, I don’t think ECP is the best choice. The other ones that I haven’t had very good success with are pseudoexfoliation eyes. I think that is because I don’t know what the hell I’m doing in there, I can’t see. Everything is white and shrunken already, so I don’t have an end point for treatment. You put the laser on there and they look the same as before you started the case.

Dr Ayyala: In the last two years I remember at least three cases that had ECP and their main complaint is chronic pain. Do you have any experience with that?

Dr Mackool: Happily none. I don’t have any patients with a chronic pain syndrome following ECP and I have done several hundred ECP procedures. The only thing I would be concerned about and I really think you need to do it in these eyes early on is to treat them as if they are going to get an iritis because as I said, five percent will. I don’t know what happens once you stir them up and get some chronic cellular infiltrate near ciliary nerves. I don’t think it is beyond the possibility that those patients could do poorly and get chronic pain, but I have nobody like that.

Dr Palmberg: When you say you back off, you’re not creating pops. You kind of wonder, maybe other people who are using the treatment more aggressively are getting the pain.

Dr Mackool: How do I know that you can get pops, I’ve done it and I have had pops. We treat them aggressively with steroids. My view about iritis and cystoid macular edema is you are much better off to prevent it by prophylactic treatment than chase it once you get it. We treat patients very aggressively that we think are at risk for these complications. For example, if the capsule breaks during surgery, if we have to do a vitrectomy, it is protocol #2. They go on hyoscine, they go on Pred Forte every two hours, and they get a lubricant ten minutes after the Pred Forte. I think you have to hit them hard and early.

Dr Ayyala: Dr Palmberg, in a patient with aqueous misdirection, how do you use a 30 gauge needle to push the IOL back?

Dr Palmberg: As I say, I have had prior cases and I did them under circumstances where the pressure was quite high and it wasn’t going to be very convenient to get the vitreoretinal surgeon there right away and so I just went in at the limbus, stayed in front of the IOL, got out to the middle of the IOL – obviously the needle is flat against the IOL – and just pushed very gently and continuously, and fluid started to come out around it and it broke the attack. But it is not going to be a cure, they were sent on for vitrectomy with an eye with a pressure perhaps of 15 to 20, not very congested and with a clear cornea so that the vitreoretinal surgeon could see what they were doing. I mention it because you may find yourself in a situation where the pressure is 80 and you want to do something to do alleviate it at the time and medicine isn’t helping.

Dr Ayyala: Do you have any experience breaking the attack by pushing the needle through the zonular area?
Dr Palmberg: No, I haven’t done that. When I could see, I have YAG’d through, the way Dave Epstein has talked about, through peripheral zonular diaphragm and the anterior vitreous and managed to get the pressure down. That will not cure the problem. The patient is going to need a vitrectomy and a unicameral eye to get rid of aqueous misdirection on a really reliable basis, so don’t think that any of those things like YAG lasering through are going to be a good solution in the long run. At least half or three quarters will recur, until somebody does a vitrectomy and takes the instrument around the IOL, through the zonular diaphragm, through the iris, into the anterior chamber and makes a connection. Then you have killed it – cured aqueous misdirection. You are not going to have it happen again.

I have one question for Dr Mackool. When you had those cases with the lens way out of position, I have usually called my vitreoretinal friends to do those cases, maybe sewing in a PCIOL. I missed how you handled the vitreous on those cases, if there is vitreous out in front of those lenses. Do you do a little small pars plana vitrectomy, pull the vitreous back and then perform the rest of the case?

Dr Mackool: If I have to. Usually, all I want to do is take enough vitreous out to get through the phaco. So first I will do the capsulorrhexis, I’ll put in the retractors, and if there is vitreous I will go over there with a little vitrector to the limbus and just clean out that area. Once I’ve got it cleaned out in that area, then I go ahead and do the phaco. The critical or difficult decisions that we don’t really have data on is what do you do after that. I have a lens that is hanging by how many zonules, 180 degrees, 90, 270. Do you go to a Cionni, do you do an Ahmed? Each one is a little different, and I factor in everything from how many eyes they have, how many zonules they have, and their age is a big factor for me. I will go to an ACL in a 90 year old in a heartbeat. Maybe in a 40 year old I might not do that, especially a 40 year old male. I am always a little concerned about young men and anterior chamber lenses. I think they live more traumatic lives.

Dr Ayyala: Dr Palmberg, do you use either 5-FU or Mitomycin-C when you needle the blebs, and if so, how do you apply?

Dr Palmberg: I think if it is at all an inflamed eye that I do use 5-fluorouracil. Most of the blebs that I needle have to have some kind of ischemic bleb, and I am not really trying to go through a thick Tenon’s wall. I don’t think needling those blebs helps much. But a bleb where you just need to pry open a scleral flap, cut some kind of a membrane that is on that surface, it’s relatively avascular. I can do that and I haven’t felt that I needed 5-FU if the eye looked totally un-inflamed. I am not sure that the problem was really scarring in an active sense of an inflamed eye. If it is inflamed, I would give 5FU depending on how red it was, perhaps at the time and perhaps two or three more times in the next week.

Dr Ayyala: Thank you, and that concludes the session.
Slit lamp procedures in postoperative glaucoma management

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Introduction

There are a variety of procedures that can be done safely and inexpensively at the slit lamp. This presentation will detail several of them.

Paracentesis using a half-inch 30 g needle

There are many clinical situations in which it is useful to perform a paracentesis with a half-inch 30 g needle held by the hub to lower the intraocular pressure in a very controlled fashion. I first apply apraclonidine 0.5% for vasoconstriction and proparacaine for anesthesia, and then prep the conjunctival sac and lashes with povidone iodide solution (Betadine). After rinsing out the povidone, the patient is positioned at the slit lamp and the lids are held open manually or with a speculum. The needle hub is grasped between the thumb and forefinger and the back of the hand rested on the patient’s cheek for stabilization. Note that the needle is used without a syringe. The tip of the needle then enters the cornea inferotemporally (Fig. 1a) in a path longer than iris parallel (Fig. 1b), so that the track will be self-sealing, enters the anterior chamber, and after ten seconds is withdrawn. Quite conveniently, the pressure necessary to force fluid through a half-inch 30 g needle is about 12 mmHg, so that the decompression stops automatically at that pressure and the anterior chamber does not flatten.

When is decompression with a 30 g needle indicated? First of all, it can be a big help in patients with pupillary block angle closure glaucoma, as it promptly relieves pain and nausea, and in most cases clears or substantially reduces corneal edema (Fig. 1c), facilitating laser iridotomy. It can also be used to promptly and precisely relieve elevations of intraocular pressure caused by intraocular injections, such as intraocular Kenalog, Macugen, Lucentis or Avastin, which are being
used to treat macular edema and/or wet macular degeneration.

Needle paracentesis has also proved useful in situations in which medical therapy could not lower the intraocular pressure (IOP), presumably due to a temporary collapse of the trabecular meshwork. Consider this example: a nine year old African-American boy had been treated unsuccessfully for three days with aqueous suppressants for a pressure of over 50 mmHg associated with a traumatic microhyphema. Gonioscopy in this very cooperative child revealed a thin, layered hyphema over the trabecular meshwork. He was scheduled for a trabeculectomy, but before going to the major operating room I instead performed a 30 g needle paracentesis in a minor OR. The pressure fell to about 10 mmHg and never rose, even after discontinuing all medical therapy. A 70 year old Caucasian woman similarly suffered a sustained elevation of IOP to 45 mmHg associated with a microhyphema from a Swann syndrome (minor bleeding from an old extracapsular cataract wound), with the pressure elevation not yielding to full medical therapy, but being promptly and permanently relieved by a 30 g needle paracentesis.

What might be the mechanism behind the pressure elevation in these cases and how can the permanent effect of the paracentesis be explained? I credit Robert Moses, MD, of Washington University in St Louis for providing evidence that a collapse of the trabecular meshwork occurs in normal eyes when the IOP rises above about 28 mmHg, giving a rationale for performing a paracentesis in such cases. In about 1972, Dr. Moses obtained fresh eyebank eyes and cannulated Schlemm’s canal with PE50 plastic tubing. He then replaced the aqueous with silicone oil and raised the IOP with a manometer connected to the anterior chamber. He measured the flow into Schlemm’s canal as he raised the IOP, and found a fairly abrupt increase in resistance to flow at about 28 mmHg. Lowering the IOP restored flow. Presumably, when Schlemm’s canal collapses, fluid can no longer pass far enough along the canal to reach the collector channels.

Back to the two cases of microhyphema – in them I can imagine that fibrin from the hyphema covered the trabecular meshwork for a day or so, causing a rise in IOP and trabecular meshwork collapse, and then the fibrin was lysed by naturally occurring tissue plasminogen activator. However, the pressure remained elevated due to trabecular collapse until the paracentesis was performed.

I have also found a 30 g needle paracentesis helpful in many cases in which the
IOP was temporarily elevated by performance of a laser trabeculoplasty, or by liberation of pigment, due to dilation in a case of pseudoexfoliation or after laser iridotomy in a chronic angle closure glaucoma patient. In some cases of open-angle glaucoma, after a period of good control the pressure may rise abruptly, for no apparent reason. One may find that after a 30 g needle paracentesis the pressure will once again be medically manageable, or at least one can lower the pressure quite a bit for the several hours it takes to get the patient ready for surgery, perhaps reducing the risk of intraoperative or early post-operative suprachoroidal hemorrhage.

Use of a 30 g needle for needling of scleral flaps, blebs and pupillary membranes, and as a spatula for freeing incarcerated iris, lysing synechiae or rotating IOLs

A 30 g needle mounted on a tuberculin syringe is a very useful needle-knife for needling scleral flaps and blebs of failing filtering procedures, and for cutting pupillary membranes.

The needle is prepared by mounting it on a tuberculin syringe and then bending it with a sterile blade breaker in two places to produce Z or bayonet configuration (Fig. 2). The bayonet shape angles the final segment of the needle about 45 degrees from the syringe, which serves as the handle of the needle-knife, allowing one to comfortably hold the syringe with the thumb and first two fingers while resting the back of the fourth and fifth fingers on the patient’s cheek for support. The Z bend in the needle allows one to keep the needle and syringe hub away from the lids.

Failing blebs can be salvaged if the conjunctiva remains mobile (as tested with a cotton tip applicator), and relatively avascular. Gonioscopy and bleb inspection will have been used to identify the site of aqueous flow obstruction. If there is a pigmented membrane blocking the internal ostium, a YAG-laser can usually apply enough energy (5-10 mJ) to cut through it. But if iris is obstructing the opening, a 30g needle is likely to be needed to tug the iris free. If the site of obstruction is an episcleral membrane, it can be punctured by passing a 30g needle into the subjunctival space several millimeters from the edge of the bleb, and

![Bent 30 g needle](image)

*Fig. 2. Bent 30 g needle.*
advancing it to the scleral flap edge or tunnel mouth (Fig. 3). Visualization of the needle tip and scleral wound may be improved by use of a Ritch or Hoskins suture lysis lens to compress the overlying conjunctiva and Tenon’s capsule (Fig. 4). The edge of a scleral flap also may be located in difficult cases by using a slit beam to illuminate the sclera next to the site, and identifying an abrupt transition where the horizontal spread of light in the sclera ends. The scar tissue in the groove at the edge of a scleral flap does not transmit light as well as does intact sclera, and appears as a gray border. The needle is passed under the edge of the scleral flap or into the tunnel mouth and used to elevate it. If the bleb does not inflate then, the needle is advanced into the anterior chamber and twisted side to side, which should restore flow to the bleb. If the bleb thus formed is rather delimited, one may use the side of the 30 g needle to cut Tenon’s capsule free from the sclera at the bleb border, thus expanding the area of filtration.
Slit lamp procedures in postoperative glaucoma management

After restoration of the bleb, the needle entry site must be Seidel tested (Fig. 3) with a wetted fluorescein strip and any leak closed by either pressure with a cotton tip applicator (to compress Tenon’s capsule, which reduces flow through it), or if leakage persists, compression may be followed by contracting the bleb tissue with a portable cautery (Fig. 3). If those measures fail, a stitch is needed, to reduce the risk of hypotony and to prevent the potential entry of bacteria.

Tenon cyst blebs are best treated medically, though if the pressure cannot be brought to a level that it is thought the optic nerve could tolerate for a few months, then needling could be attempted, and this has been reported to be more successful if an antimetabolite is applied prior to or with performance of the needling.

A 30 g needle may be used to tug iris out of the filtering ostium when it prolapses at the time of laser suture lysis. Since there will no longer be a pressure gradient between the anterior chamber and the bleb, once the iris is freed it is not very likely to prolapse again. In Figure 5a, the pupil is seen to be updrawn by iris incarceration in the filtration ostium. In Figure 5b the 30 g needle engages the iris. In Figure 5c the iris is being pulled down. In Figure 5d the iris has been freed, the pupil is round and one can see the iridectomy above.

A 30 g needle may also be used to cut a pupillary membrane (Fig. 6), especially when the membrane is thought to be too thick to cut with a YAG-laser. In the case illustrated, a thick membrane formed in the pupillary space of a diabetic and iris was incarcerated in the internal ostium of a trabeculectomy, the latter causing the IOP to be elevated despite the presence of an ischemic looking bleb. A 30 g needle was used to cut and tear the membrane circumferentially, opening the pupil, and the needle was also used to tug the iris free from the internal ostium. Fresh fibrin strands formed between the iris and the needle entry site after the procedure, but dissolved spontaneously during the next two days. The patient then saw 20/20, and had a pressure in the low teens.
Use of a 30 g needle as a spatula to rotate a sunseted IOL back into the capsular bag

In the case illustrated (Fig. 7), one haptic of a PC IOL had passed through the capsular bag, allowing the lens to sunset half-way in the pupil, and iris was incarcerated in the trabeculectomy ostium, with an IOP of 30 mmHg. At the slit lamp, after applying iopidine, proparacaine, Betadine solution and rinsing, a 30 g needle was used to test the mobility of the PC IOL, and, when it was found to be freely mobile, the lens was rotated clockwise 90 degrees to bring the haptic back into the capsular bag in a horizontal orientation, and also to tug the iris free from the internal ostium, restoring the bleb.

Fig. 7. Rotating PC IOL back into bag.
Slit lamp procedures in postoperative glaucoma management

Use of a 30 g needle as a spatula to push a PC IOL posteriorly, breaking an attack of malignant glaucoma

On a Friday afternoon at six o clock, after three days of medical treatment with aqueous suppressants and topical atropine for aqueous misdirection glaucoma, the IOP was 80 mmHg, the anterior chamber very shallow and the cornea very edematous in a pseudophakic eye (Fig. 8). The cornea was too opaque to laser the posterior lens capsule in the periphery, nor was an iridectomy seen through which one might laser the zonular diaphragm. After applying iopidine, proparacaine, betadine solution and rinsing, a 30 g needle was used to decompress the eye to about 12 mmHg. Then a second 30 g needle was bent into the shape of a bayonet and mounted on a tuberculin syringe. It was passed through the cornea to enter the anterior chamber just at the pupil margin, and then used to gently push posteriorly on the superior portion of the PC IOL. As the PC IOL moved posteriorly, fluid began to flow forward through the pupil into the anterior chamber, deepening it and opening some of the peripheral angle. On the following Monday the patient underwent definitive treatment with a pars plana vitrectomy and passage of the vitreophage through the zonular diaphragm and iris superiorly, creating a unicameral eye. At the time of the operation, the cornea was much less edematous, the eye less congested and the pressure was 30 mmHg. Reformation of the anterior chamber at the time of the vitrectomy normalized the IOP. This procedure has been successful in breaking an attack of aqueous misdirection in five of six cases, but has been employed only when immediate relief of a very high IOP was indicated or a vitreoretinal surgeon was not readily available. I would suggest aborting such a procedure if release of fluid from behind the IOL were not noted with a small displacement of the IOL, so as not to produce a zonular dialysis.

Fig. 8. Breaking attack of aqueous misdirection glaucoma with 30g needle.
Use of a 30 g needle to inject Tissue Plasminogen Activator to dissolve a blood clot filling a bleb cavity, or blocking a filtering ostium or the tube of a glaucoma drainage device

When a blood clot obstructs a filtering ostium or fills a bleb cavity, or blocks a drainage implant tube, Ativase 10 micrograms (Tissue Plasminogen Activator) may be injected into the anterior chamber to lyse it (Fig. 9). The anterior chamber is first decompressed with a free 30 g needle, and then 0.1 ml containing 10 micrograms of tissue plasminogen activator is injected into the anterior chamber. In approximately 20 minutes the blood clot will be substantially dissolved and the obstruction resolved. In the illustration, a blood clot in a rubeotic eye was obstructing the tube of a Baerveldt Glaucoma Implant. The tube had been ligated with 7-0 vicryl and fenestrated twice with an Alcon TG 160 needle. After lysis of the clot, the pressure became controlled.

Fig. 9. Injecting TPA for Clot.

Use of a TG 160 suture needle to re-fenestrate a ligated Baerveldt Glaucoma Implant tube at the slit lamp

When the IOP rises during the first two weeks after placing a ligated Glaucoma Drainage Device (Baerveldt or Molteno), one may re-fenestrate the tube (Fig. 10) by passing a TG160 needle (from a 7-0 vicryl suture) through the conjunctiva at the slit lamp.

At two or more weeks, the ligature may be cut with an Argon laser with a 50 micron spot, 0.5 w for 0.5 seconds (Fig. 11). This is facilitated by having placed the knot of the ligature on the back of the tube so that only a single strand of suture needs to be cut.
A patient with rubeotic glaucoma presented with an IOP of 50 mmHg on full medical therapy, despite previous surgery to place a 350 mm² Baerveldt Glaucoma Implant superior temporally and a full pan-retinal photocoagulation. The tube tip was not obstructed in the anterior chamber, but a thick capsule had formed over the implant reservoir. It was elected to place a second 350 mm² Baerveldt Glaucoma Implant inferior nasally, with the tube just in front of the iris. Several weeks later the ligature dissolved and the pressure was well controlled at first.

However, at two months after placement of the second implant, the iris contracted and engulfed the tip of that tube. Gonioscopy revealed that one could see the back surface of the iris draped over the tip of the implant tube (Fig. 12). Therefore, a laser iridotomy was performed through a gonioprism, using a 50 micron Argon spot at 1.0 watts and 0.1 seconds. This freed the tip of the tube and restored drainage, with a final IOP of 8 mmHg.
Use of a 30 g needle to inject Healon V and perform goniosynechiolysis to salvage an angle closed after vitreoretinal surgery with either silicon oil or gas

 Occasionally after vitreoretinal surgery with use of silicone oil or gas to fill the vitreous cavity a form of pupillary block glaucoma will occur, despite placement of an inferior iridectomy at the time of vitreoretinal surgery. When withdrawal of some of the silicone oil or gas does not result in reformation of the anterior chamber, potential disaster awaits. If firm posterior synechiae are allowed to form, then one will be faced with uncontrolled glaucoma and no anterior chamber. There is then no space in which to perform either filtering surgery or placement of a glaucoma drainage implant. In addition, deprived of nutrition, the cornea will soon decompensate as well.

 In two such cases, after the vitreoretinal surgeon aspirated some of the silicone oil or gas through the pars plana and the anterior chamber did not reform, we reformed the anterior chamber at the slit lamp by injecting Healon V circumferentially in the far peripheral angle to wedge the iris away from the cornea (Fig. 13), with supplemental goniosynechiolysis with the 30 g needle tip to pull open

 Fig. 13. Collapsed AC after intravitreal gas.
those portions of the angle that remained closed. Thereafter, aqueous joined the injected Healon V to further deepen the anterior chamber. We had anticipated needing to rinse out the Healon V with Balanced Salt Solution once the anterior chamber reformed, but in neither case did the pressure rise again either then or over a several month follow-up.

Summary

Thus, there are many situations in post-operative glaucoma care in which slit lamp procedures may solve problems in an efficient, safe and inexpensive manner. You can be Micro Zorro (Fig. 14), in imitation of the legendary swordsman who saves the day for those in distress.

Fig. 14. Micro-Zorro.

References

Round Table

Surgical choices: Trabs, tubes and Betadine

Moderator: Paul Palmberg, MD, PhD
Panel: James Gills, MD
Peng Khaw, MD, PhD
Eve Higginbotham, MD
Kuldev Singh, MD

Dr Singh: What are your criteria for placing an inferonasal tube? I have relaxed my criteria. I look for excuses to place an inferonasal Baerveldt for several reasons. Do you want to comment on that?

Dr Palmberg: Yes, obviously one reason is that if someone has had a superior filter and it is all scarred, you are going to be dissecting through all kinds of tissue and even though that may not be the filtration area, it’s a lot of work. Going through virgin inferior conjunctiva means less blood and inflammation. I also think the inferior tissues are thinner and that may lead to higher success. In addition, the Baerveldt now has fenestrations in the plate so diplopia is less of a problem. Inferonasal may be the preferred location.

Dr Singh: Inferonasal tubes perform extremely well and what is amazing is how easy the surgical technique is.

Dr Palmberg: Technically, it is much easier. I would agree with you, because you are looking down into the quadrant you’re working in instead of trying to figure out what’s going on in the superior quadrant under you. You don’t have to pull the eye so far, and you are probably less likely to get ptosis. Yes, I think it is very good for a number of reasons and I think many of those have been mentioned. But if you’re going below, there is one thing that I think is very important, and that is, look at the lower lid position. Because if the scleral or corneal patch is going to be right up to the edge, it will interfere in tear flow, which is coming along your lower eyelid. I want to be sure that I get three millimeters behind the limbus on these cases and burrow up with a 23-gauge needle so that I can put my patch two full millimeters behind the limbus so that the lid position will not be interfered with. Otherwise, you are going to have problems with tearing and pooling of tears. So that’s the only thing that I think is a special precaution for going down below.
**Audience:** If you can’t visualize a suture for laser suture lysis no matter what, do you have any tricks?

**Dr Higginbotham:** Well, that’s a good question. I generally will try the Hoskins. If that doesn’t work, then I use a side of a gonio mirror as another option. The Zeiss or the Posner works well, because you can apply more pressure.

**Dr Singh:** You can always see the suture. You might ask how that can be. If you think you can’t see the suture, you go to your iridectomies where you did the flap, you take a Hoskins lens and you push with a little bit of pressure right on where the flap should be and just sit there for as long as you need to. Eventually it will squeeze everything else out of the way and eventually you will see the suture well enough to cut it. If you can’t – I’ve never had a case in my entire career where I couldn’t cut the suture at the slit lamp – but if it did happen, I think you could use a needle. You could go subconjunctivally with a needle and feel your way to where the stitch should be and cut it.

**Dr Higginbotham:** Never say never. There are times when you can’t see the suture.

**Dr Palmberg:** It happens much more often when somebody has had previous surgery with previous scarring and a scleral flap that’s way back of the limbus. Tenon’s gets thicker the farther back you go. That is one reason that I use these short little tunnel incisions. I can always see the stitch because the Tenon’s is not very thick near the limbus. One other thing about the tunnel incision is you can see those nylons inside and you can laser them through a gonioprism. If you anticipate that you will have difficulty finding a stitch then place releasable sutures. Or, you can do what I just described and aim the laser using a gonio lens through the translucent scleral flap and cut the stitch.

**Dr Khaw:** I think one of the advantages of the adjustable suture is that you can always see the suture. Even if you have a thick wad of blood there, you use the forceps and you very gently just push down on there, you can always see the sutures. Once you have seen them, you can then do what you need to, because you don’t need visualization.

**Dr Singh:** I think I should qualify my comments. There are people you just can’t do suture lysis on. You can’t do suture lysis on small babies that can’t sit at the slit lamp and have you do suture lysis. There are patients whom I pre-select, patients not be able to sit still for suture lysis. But having said that, blood has never been an obstacle. Tenon’s is not an obstacle because I cut Tenon’s out of the way if there is enough to obscure suture lysis efforts.

**Dr Palmberg:** With lower diffuse blebs, are you willing to allow patients to wear contact lenses? If so, do you suggest a large soft lens or a small rigid lens?

**Dr Singh:** I have a dozen patients who have had blebs for over five years that have been wearing contact lenses. I generally have them use soft contact lenses. I worry about the rigid ones that move, the edge may be affecting the bleb. I am less concerned about a large soft lens that partially covers a low diffuse bleb.
Surgical choices: Trabs, tubes and Betadine

Dr Khaw: I think one of the things about doing the technique where you get a diffuse bleb, you do have a chance. Like Kuldev, I am actually very unhappy about my patients using contact lenses, but if they are high myopes and they have needed drainage then I will aim for as posterior a bleb as possible. I’ll enhance that technique so I get a very posterior bleb, and then if they are really desperate then they can use soft lenses. These patients definitely have a bottle of topical antibiotic to take with them wherever they go.

Dr Palmberg: What I do in these patients if it’s really critical to wear a contact lens is do a tube and I come in way back and I don’t have to worry about it, if it’s critical.

Dr Palmberg: How do you treat an early postoperative leak?

Dr Khaw: I know it seems hard to believe, but with the current closure we very rarely get early postop leaks. If we detect a leak in the presence of a bleb, we will observe it for a week or two and in virtually all the cases it will seal. If the leak persists, and this is very rare now, then I will take them back to theatre and put a stitch in, but I have to say that’s incredibly rare. I haven’t done any in the last two or three years.

Dr Higginbotham: Certainly it is going to be dictated by the size of the leak. If the leak is minimal, then you may be able to get by with just reducing the steroids. If the leak occurs in the first three weeks or so, then I add an antibiotic ointment. If that doesn’t work and if it is a larger leak, then you may need to take the patient back. Because you really do want to get that flow going, as we learned from the 5-FU study.

Dr Palmberg: Yes, if the bleb is collapsing, you’d better do something.

Dr Singh: I think the size of the leak is important, but I find the size of the bleb is more important. If you have a leak and a bleb, I’m less concerned than if I have a leak with no bleb. If the bleb is flat early in the postoperative period for a few days, I will go back in and fix that leak, just so that the bleb will be reforming.

Dr Palmberg: Peng, I have been thinking about your new technique with the corneal slits and I realize this may be a way of solving a problem that I’ve had. It has seemed to me that the reason these early leaks occur is because the conjunctival-sclera bites are not vertical and are not aligned. A skimpy tangential bite causes a tear and becomes loose at the limbus. Using your technique, the bite is coming through the groove up vertically, going up through conjunctiva, across, and vertically down.

Dr Khaw: Yes, you get very good apposition if you use that.

Dr Palmberg: So, that’s brilliant, you’ve helped me again.

Dr George Ellis: I was interested in endophthalmitis and endophthalmitis prophylaxis. I heard Dr Gills say he was using Betadine before his cataract surgery and
at the end of the case for his cataract surgery. Are the glaucoma people doing that in their glaucoma operations also?

Dr Higginbotham: Well, I obviously prep the eye, but I just give patients subconjunctival gentamycin and Maxitrol ointment at the end of the case.

Dr Ellis: Dr Gills, you are using topical Betadine, is that correct?

Dr Gills: Yes, because I am worried about the conjunctiva. I use a lower dose and use it more often. Because the dosage that most people use is far excessive of what’s been necessary. I think it is very important to use it once or twice, in some cases, to use Betadine after surgery. I think the draping to get the lashes out, treatment of any preoperative meibomian gland disease with oral doxycycline and hot compresses and getting that under control could reduce the risk in glaucoma filtering surgery where you are going to have a bleb afterwards.

Dr Palmberg: Do you use the antibiotic solution to hydrate the cornea as well as refill the anterior chamber and for how long is eye rubbing important to avoid after cataract surgery?

Dr Gills: I’ll make everybody hate me. I say, keep your hands away from your eyes and your face and you will be a lot healthier. I tell all my patients, keep your hands away from your eyes, because it is really just poor hygiene to rub your eyes.

Dr Palmberg: When you are hydrating the cornea, do you use the antibiotic-containing solution, so it’s in that wound?

Dr Gills: I used to. I don’t do it as much now, because I use the solution that goes into the vitreous now that has the antibiotics in it. What I am using now is BSS.

Dr Palmberg: Howard Fine, I think, made a very important point. If you are doing a cataract combined or separately on an eye that has a bleb, or going to have a bleb, with a pressure of 10, don’t do sutureless surgery. Because this valve-like effect that’s present when you have pumped up the eye is going to go away when the pressure goes down to 10, the cornea incision will open and you have a real risk of infection. Howard Fine points out that it is important to place a 10-0 nylon in your wound. What you want to do is sew the top and bottom of the tunnel together. If you happen to get a leak associated with a wound burn, you can take a bite that goes horizontally from the side of the tunnel down through and up, that just closes the internal aperture, not a radial stitch but a horizontal one. It will put the top and bottom of the tunnel together and that will fix that kind of leak.

Dr Khaw: Could I make a point about the Betadine. Povidone iodine, as we call it in the UK, is the only proven thing to prevent endophthalmitis. Antibiotics haven’t been proven to, but certainly Betadine has. The reason I like povidone iodine, is because it kills organisms very quickly. For all needling procedures or interventional procedures in the clinic, we use it. We definitely use it preoperatively because if you have stuff on the lashes, antibiotics won’t work quickly enough for you to sterilize the field before you do surgery. The final thing which is also
Surgical choices: Trabs, tubes and Betadine

very useful is, if you have a blebitis and you have a little focal element of infection there – you can see sometimes it looks purulent – then you can place one drop of povidone iodine in and that sterilizes the area very quickly. You have to put anesthetic of course, because it stings. And that’s a very quick way of getting on top of a purulent conjunctivitis, because you kill the organisms instantly as opposed to waiting for antibiotics to work after a few hours.

Dr Ellis: Dr Quigley stated that he does not use postoperative antibiotics. Fifteen years ago I stopped using postop antibiotics for my strabismus cases because I figured there was very little chance of getting a postop infection. But the community is using postop antibiotics, and I am wondering what the panelists are doing in their postoperative patients. If you could ask each one individually, I would appreciate hearing the comments.

Dr Gills: I don’t use them; my son uses them just because the community uses them. I think it is your choice how you want to do it. There are no statistics, as Harry will point out, that show there is any benefit in postop drops in cataract surgery.

Dr Higginbotham: As I mentioned, I don’t, besides just using the ointment at bedtime, the antibiotic steroid ointment, because it is just another insult to the eye. Certainly, if they are going to get endophthalmitis, it is either going to be because of the bleb that might be leaking or because there is a hole in the eye. I generally don’t use an antibiotic postoperatively, besides the ointment.

Dr Singh: I use the antibiotic. The lesson here is the more prominent you are as an ophthalmologist the less likely you have to do things to defend yourself from attorneys, and these two on my right are prominent enough to not do it. Because the reality is, there is no evidence to show that post-operative antibiotic drops protect against the development of endophthalmitis. If you have a patient that has endophthalmitis – the community determines the standard. You need experts or prominent people to get up on the stand to tell the judge that there is no evidence in support. I just don’t want to go through the hassle of that. I currently use a fluoroquinolone for a week q.i.d.

Dr Khaw: I have a comment based on an anecdotal impression. I have had two patients who developed corneal ulcers with bacteria that would have been sensitive to the antibiotic I normally use, so for that reason alone, I always use antibiotics.

Dr Palmberg: If I do use it, I think of benzalchromium chloride in the Pred Forte every two hours as being almost like giving povidone iodine over and over again.

Audience: What do you do if the patient says they are allergic to iodine? Do you use Betadine solution or do you use a substitute?

Dr Palmberg: It depends upon what caused the allergy, if it was the soap then I use pHisoHex.
Dr Singh: I don’t use Betadine in case they have an iodine allergy, because I think if they have a problem they are going to blame it on the iodine.

Dr Palmberg: I want to thank the audience and panel for providing an informative discussion.
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