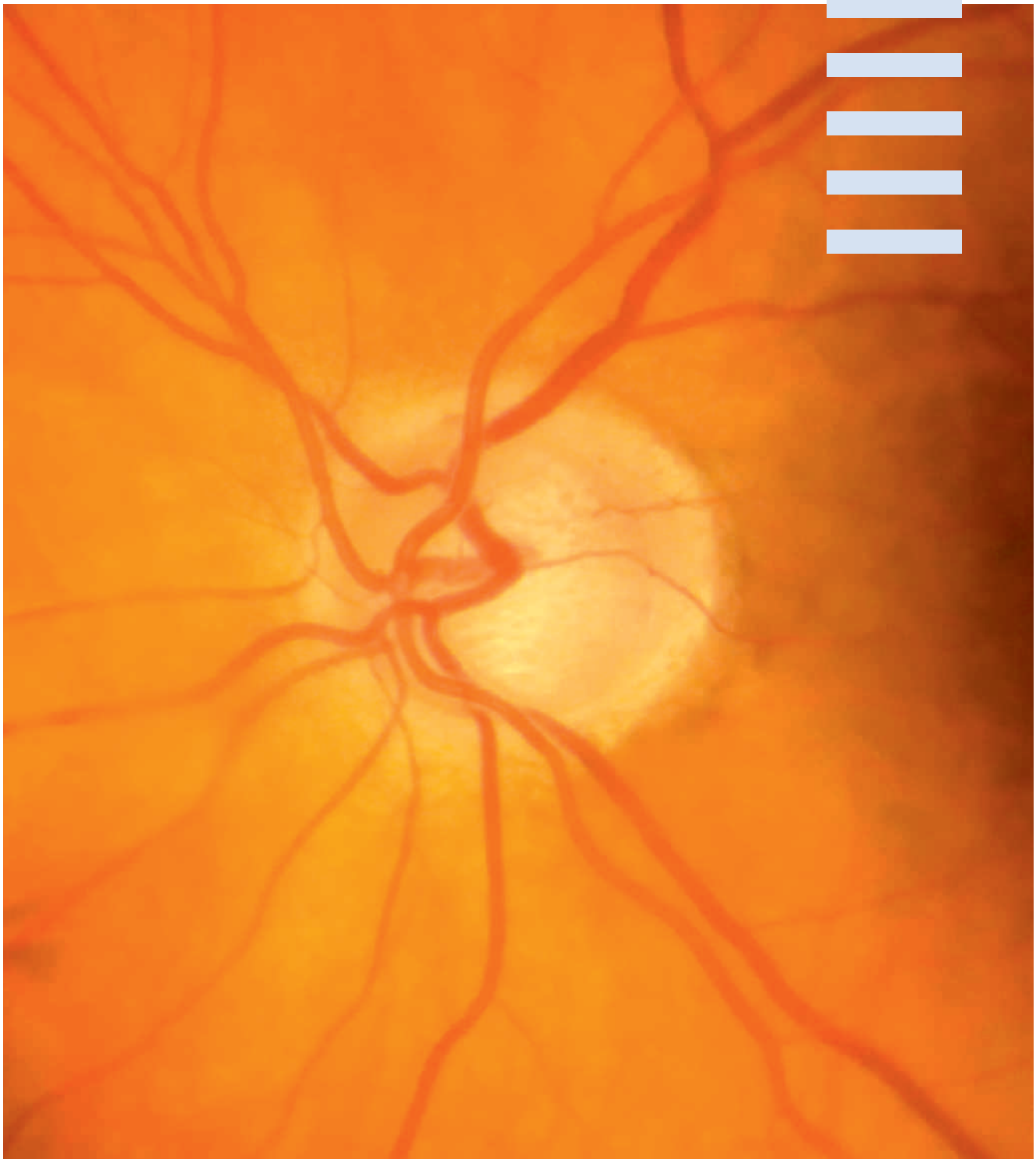
Supplement to
AUSTRALIAN OPTOMETRY

Special issue GLAUCOMA

pharma

JUNE 2012



- Expanding role of optometry
- IOP elevation
- Angle closure
- Technology
- Boosting mitochondria
- Neovascular glaucoma
- Aflibercept and AMD
- Needleless injection

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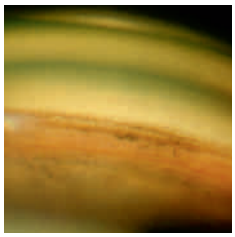
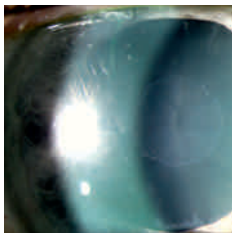
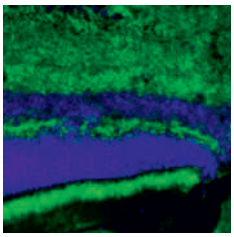
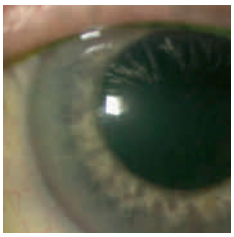
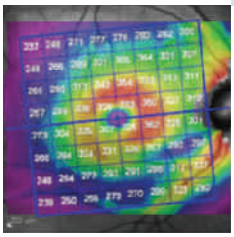

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Glaucoma

The expanding role of optometry

Clinical Editor's viewpoint

Associate Professor Mark Roth
Clinical Editor, *Pharma*

The American Society for Cataract and Refractive Surgery (ASCRS), a 9,000-member international society of anterior segment surgeons, has announced the establishment of a new membership category that will enable optometrists, for the first time, to apply for membership of the organisation.

The new membership category emphasises a working partnership between ophthalmologists and optometrists and supports an integrated model for the delivery of health-care to the millions of Baby Boomers rapidly approaching retirement age.

When asked why this new arrangement was so important, the outgoing ASCRS president, Dr Edward Holland MD, said the present eye-care delivery model was unsustainable. 'We will simply not have enough ophthalmologists to perform all eye-care needs that will be required, both medical and surgical. One solution to this pending crisis is to become more efficient at what we do. An ophthalmologist-led model will allow a gradual transition of non-surgical eye care to optometry in order to support a more efficient ophthalmic surgeon,' he said.

While there is a world of difference between the American health-care system and that of Australia, the ASCRS's move to welcome optometrists is instructive.

By acknowledging the importance of optometry in managing the health-care demands of the increasing number of Baby Boomers moving into their 60s, the organisation points a way forward and illustrates the importance of further co-operation between ophthalmologists and optometrists in Australia.

Optometrists are the first point of contact for most eye-care patients and account for the majority of referrals of cataract and glaucoma patients to ophthalmologists. As never before, optometrists are drawing on new technologies to examine the optic disc, nerve fibre layer and visual fields. These new technologies, together with a comprehensive examination, yield more information about the state of the patient's eye and lead to more reliable diagnoses.

Early detection of glaucoma or other eye diseases should be the cornerstone of any eye examination. As Glaucoma Australia points out on its website, the statistics on the disease are alarming. Glaucoma is the leading cause of irreversible blindness worldwide and one in 10 Australians over 80 years will develop glaucoma. Despite these numbers, about 50 per cent of Australians with glaucoma are undiagnosed.

The optometrist's ability to provide accurate referrals or initiate appropriate management is enhanced by the sharing of knowledge across the professions. It is the opinion of many optometrists, including me, that the expertise demonstrated by therapeutically-endorsed optometrists provides a foundation for involvement in patient care that moves beyond the traditional role of detection and referral. Progressively, the profession of optometry will define itself not only in the early detection of eye diseases such as glaucoma but also in their treatment and management.

This is where I believe *Pharma* comes in. Our last issue had a special focus on new developments in cataract surgery, recognising the need for optometrists to stay informed of the latest surgical technology that their patients may experience. Because more optometrists are involved in the management of glaucoma patients, we produce an annual glaucoma issue recognising that the knowledge of emerging evidence, new technologies and advances in the drugs involved in the treatment are becoming more important than ever before. We have major advances in technology but technology alone does not diagnose glaucoma; it is the increased expertise of the optometrist to examine the patient and analyse additional data that makes for effective diagnosis and management. This expertise requires a commitment to life long learning. Hopefully, *Pharma* contributes to this goal. ■

Unsuspected IOP-elevating activities

Eye wiping, playing a trumpet, wearing goggles, strenuous effort and even just lying down can cause IOP to rise

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The two governing pathophysiologies in glaucoma damage are mechanical failure of load-bearing connective tissues of the optic nerve head (ONH) and progressive damage to the adjacent axons (with eventual retinal ganglion cell death) by a combination of both compressive and ischaemic mechanisms.[1] Responses of the optic nerve/lamina cribrosa complex to IOP elevation have been demonstrated experimentally in porcine eyes.[2] Mechanical failure occurs as the level of strain exceeds the elastic limits of the ONH tissue and IOP may be physiological or patho-physiological, depending on the ONH capacity to withstand stress.[1]

Elevated intraocular pressure (IOP) is a positive risk factor for the development of glaucomatous optic nerve damage and visual field loss.[3] To explain progressive changes in the optic disc in glaucoma, one plausible hypothesis is that acute IOP spikes or transient elevations, which are undetected during routine clinical examination, lead to disease progression.[4,5]

In a 13-year study of patients whose IOP was maintained at low levels, larger long-term visit-to-visit fluctuation of IOP was associated with significantly higher visual field defect scores.[6] Similarly, field losses might develop or be exacerbated by IOP fluctuations associated with unsuspected IOP elevating activities. From examination to examination in a longitudinal study (mean fluctuation of 3.16 ± 1.35 mmHg for those who progressed to glaucoma),[7] fluctuations that occur with normally innocuous day-to-day activities are not detected. The IOP elevations that have been recorded during some activities are shown in the Table (right).

Bjorn Russell surveyed 100 consecutive patients and found that the most prevalent intraocular elevating activities reported were:

- eye rubbing daily 47%, hourly 9% and more than hourly 1%
- watery eyes wiping daily 17%, hourly 5%, more than hourly 1%
- prone sleeping weekly 11%, daily 32%
- physical exercises weekly 28%, daily 17%.

That IOP elevating activities may have pathological significance is suggested by the finding that the greatest difference in IOP between sitting and supine positions was observed in the worse eye of patients with primary open-angle glaucoma.[8] This finding suggests that damage to the optic nerve in primary open-angle glaucoma might occur when patients are asleep in the supine position.[8] As indicated in the Table (below), IOP may be elevated to much higher levels by activities other than a supine body position during sleep. Depending on their duration, some may have correspondingly greater pathological significance.

The ONH is constantly under IOP distending stress and the threshold level for pathological changes will depend on individual optic nerve susceptibility.

Continued page 4

- Light touch through adnexal skin or lids (eye wiping, pillow contact): approximately doubles baseline IOP[21]
- Eye rubbing or massage (warm compresses): elevations up to 306 mmHg[22] and 400 mmHg[23]
- Short duration (30-minute) supine body positions: mean elevation of 4.4 mmHg[24]
- Long duration prone body positions: mean elevation of 40 mmHg[25] especially for overweight or obese patients[26]
- Inverted body position (yoga): mean elevation of 36 mmHg[27]
- Playing loud, high-pitch notes on a high wind-resistant instrument (trumpet et cetera): elevations up to 44 mmHg[28]
- Wearing swimming goggles in a sitting position: elevation up to 48 mmHg[29,30]
- Strenuous muscular effort (push-ups, bench presses et cetera): elevation up to 30 mmHg[30]

Intraocular pressure elevations recorded during a range of activities

Unsuspected IOP-elevating activities

From page 3

If susceptibility to IOP distending stress is high enough, normal tension might be sufficient to induce pathological changes although, in such cases, unsuspected IOP elevation activities are possibly even more likely to have pathological significance.

In addition to individual patient susceptibility, the pathological significance of IOP elevations will also depend on elevation episode frequency, duration and long-term history, apart from or in combination with the level of elevation. For example, the time-dependent nature of responses to elevated IOP was demonstrated in monkeys using confocal scanning laser tomography.[1] The lamina cribrosa was found to displace posteriorly with elevated IOP, but with chronic IOP elevation, the displacement was eight times more than with elevated IOP alone.[1]

As IOP remains the most important risk factor in glaucoma and because its fluctuation seems to play a role in the disease development and progression, even in cases of statistically normal pressures,[3,9-11] it may be prudent to include a wider consideration of the possible role of frequently unsuspected sources of IOP elevation in the management of this disease. Unsuspected IOP elevations that are usually innocuous may help explain some cases of optimum treatment (including full compliance with medication and seemingly good control of daytime in-office IOPs) that are nevertheless associated with unchanged rates of disease progression.

The great variation in glaucoma progression rates across diagnostic groups and also among patients in the same diagnostic group[12] may be explained in part by variable exposure to unsuspected IOP-elevating activities. The treatment of ocular hypertension has been problematic in the few decades since it was recognised[13] and a decision to not treat might be easier when a history of possibly significant exposure to activities that elevate IOP provides an opportunity for advice to be given that results in a reduction in those activities and the associated exposure to IOP elevations.

A patient's history of IOP-elevating activities revealed by the exploratory screening used in this study* would require discussion of findings to improve an estimate of the degree of exposure. For example, the frequency and duration of activities in which they engage and other factors that are not evident from the screening would need to be considered.

To illustrate the point, consider patient 2 in this series (male aged 63 years, IOP R: 18 mmHg L: 20 mmHg) who reported rubbing his eyes using two fingers under his spectacles several times a day, the right eye much more than the left eye. The rubbing was prompted by blur in the right eye due to diabetic maculopathy and oedema, evident with ocular coherence tomography (Zeiss Cirrus HD-OCT). He also reported watery eye wiping daily, also right eye more than left. A suspect right superior nasal step field defect (Figure 1) corresponds with the reported greater exposure to rubbing and wiping IOP-elevating activities for the right eye. He was also found to have a thinner than average retinal nerve fibre layer thickness of 67 µm, in the right eye (L: 85 µm). There was greater thinning inferiorly in the right eye, corresponding to the suspect field defect (Figure 1). Anterior chamber angles were moderately wide open in both eyes, nasally and temporally. The findings in the right eye contrast with the apparently

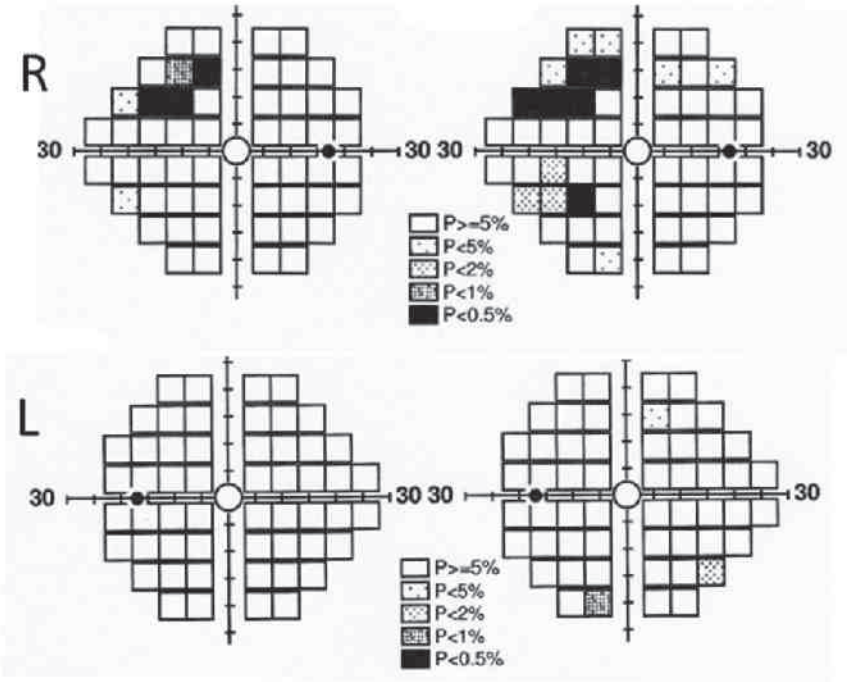

Figure 1. Suspect field defect for patient 2

normal findings in the left eye. It is possible that his history of asymmetric rubbing and wiping could have a contributory role if there is further development of the suspected glaucoma.

Preference for rubbing or wiping one eye more than the other may be reflected in a corresponding asymmetry of pathological change.[14] Case reports describing unilateral diseases, which develop following exposure to a putative causal factor for those diseases, may have the potential to provide higher evidentiary significance of causality.[14] The unaffected eye in these cases acts as a control for the affected eye, providing a basis for inferring a similar unaffected status for the affected eye, if it had not been exposed to the putative causal factor.[14]

Glaucoma progression risk has been found to decrease by about 10 per cent with each millimetre of mercury of IOP reduction from baseline.[15] IOP fluctuation was found to be a risk factor for visual field loss progression in the Glaucoma Progression Study.[16] After a review of inter-visit IOP fluctuation as an independent risk factor for glaucoma, the conclusion was drawn that practitioners should consider whether patients who are progressing at low mean IOP may benefit from having IOP variation reduced.[17]

Lack of disease progression after cessation of IOP elevating activities in cases of glaucoma has been reported,[18,19] prompting the question of whether in the absence of any apparent adverse consequences associated with such precautionary advice, management of patients with or at risk of developing glaucoma should include recommendations to modify, avoid or reduce IOP-elevating activities. Application of suggested changes to the behaviour patterns of patients may be considered if lifestyle alterations are not harmful, even if the benefit is not confirmed by stringent tests of study design and statistical significance.[20]

* The survey questions used to screen for unsuspected IOP-elevating activities are available from c.mcmonnies@unsw.edu.au.

Even in cases of statistically normal pressures, it may be prudent to include a wider consideration of the possible role of frequently unsuspected sources of IOP elevation in the management of this disease.

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Are you missing angle

Dr Lance Liu
MBBS FRANZCO

Over the past 40 years there have been many advances in the field of glaucoma. The definition of glaucoma has changed from its emphasis on IOP to a progressive optic neuropathy. Numerous glaucoma epidemiological studies have shown primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG) exist in all populations. POAG is more common in the Caucasian population[1] but the incidence of PACG is greater in people from Asia. Coupled with this were many studies showing the various risk factors associated with the development or progression of POAG.

Given Australia has an exceptionally diverse multicultural population, a correct diagnosis of the clinical type of glaucoma is essential. The dichotomy of 'open angle' versus 'closed angle' glaucoma is based on the findings of gonioscopy (Figure 1). Gonioscopy is currently the gold standard in assessing the anatomy of the anterior chamber angle; its clinical appearance is vital as it determines which management path the patient must follow.

Being aware of angle closure is simply not enough, as now we need to exclude PACG before making a diagnosis of POAG.

Glaucoma is currently defined as progressive optic neuropathy, characterised by damage to the optic nerve, nerve fibre layer and/or typical glaucomatous visual field changes where IOP is a risk factor. POAG may be more commonly diagnosed for a number of reasons; however, recent advances in PACG are challenging our current thinking.

- Currently, screening tests such as Van Herick, flashlight test or measuring the central anterior chamber depth are used to detect angle closure. With a negative result, one could assume the angle was 'open'; however, these tests have shown to be neither sensitive nor specific enough in detecting angle closure. Assessing the angle using the Van Herick method or measuring the central anterior chamber depth has a 61.9 per cent[2] and 75 per cent sensitivity, respectively.
- Peripheral anterior synechiae (PAS) or synechial closure is pathognomonic of PACG; therefore, one may incorrectly conclude that the absence of PAS implies the angle is 'open'. Apart from synechial closure, the IOP rise in PACG can also be caused by appositional closure and damage to the trabecular meshwork (TM). Consequently, although synechial closure is easily diagnosed, appositional closure is commonly present when the pupil is physiologically dilated in the dark.[3] This can be missed when the light used to examine the angle constricts the pupil and opens up the angle that is closed in the dark. (Figures 2A and 2B)
- Many of the epidemiological studies show that POAG is more common than PACG; however, this observation varies with the definition of PACG used in these studies. It is taught that as long as the TM is seen in at least one quadrant with gonioscopy, the angle is classified as 'open'. This definition of an 'open' angle is liberal as it means that it requires three quadrants or more of angle closure (unable to see the TM) before it is classified as 'closed'. Given that the rise in IOP can be due to TM damage[4] as well as synechial and appositional closure, it is now thought that having at least one quadrant of closure is needed before the IOP can be affected.[5]
- Finally, there is a poor performance and documentation of gonioscopy in the clinical setting. This is compounded by the fact that there is much variability when assessing the

Figure 1. The appearance of the angle with gonioscopy Photo: Dr Liu

closure?

Primary angle closure glaucoma is likely to be misdiagnosed and underdiagnosed

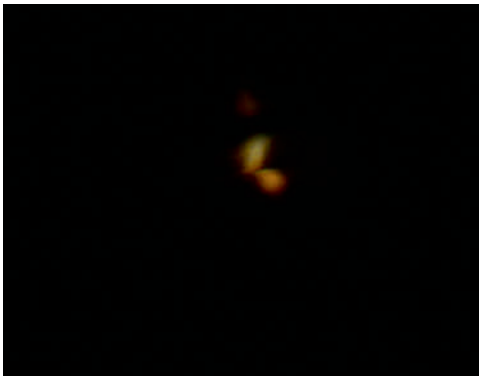

Figure 2A. The angle is closed when examined in the dark with a small slitlamp beam in a completely dark room Photo: Dr Liu

Figure 2B. In the same patient, the angle is open when examined with a large slitlamp beam Photo: Dr Liu

angle, depending on the lighting and tilting of the goniolens. A survey of Australian and New Zealand ophthalmologists showed that 56 per cent perform gonioscopy in over 50 per cent of their glaucoma patients but only 13 per cent would repeat it on the same patient.[6] Thus, we may have become complacent in diagnosing the patient's glaucoma as 'open angle', even when gonioscopy was not performed to confirm the diagnosis.

It is probable that PACG has been underdiagnosed or misdiagnosed, especially where appositional closure has been missed. Given that PACG is a treatable anatomical disease, all of the current glaucoma guidelines now state that gonioscopy should be performed to exclude angle closure.[7] Therefore, an 'open angle' has become a diagnosis of exclusion. This is a large paradigm shift away from assessing whether the angle is 'open'.

To assess whether the angle is closed, one needs to understand first the pathophysiology of angle closure. Angle closure is characterised by iridotrabecular contact (ITC). The risk of ITC depends on the height of the iris plane relative to the trabecular meshwork and degree of physiologic pupil dilation.[8] ITC is more commonly found when the pupil is physiologically dilated and in the superior rather than inferior angles. It is characteristic of synechial and appositional closure, which can cause blockage of and damage to the TM[4] leading to a rise in IOP.

To determine whether the angle is 'closed' with gonioscopy, the following guidelines may help.

- In a completely dark room, examine the angle to identify the anatomical landmarks (scleral spur or Schwalbe's line) with a goniolens (Figure 3) with a wide slitlamp beam.
- Look for signs of synechial closure or PAS (Figure 4). Its insertion can be classified as 'high' (at or above the pigmented TM) or 'low' (below the pigmented TM).[9]

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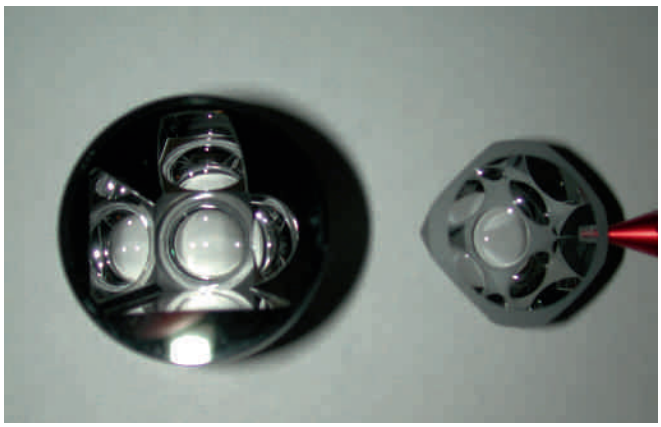

Figure 3. Two types of gonioprisms used to assess the angle; Goldmann three-mirror (left) and Posner four-mirror (right) Photo: Dr Liu

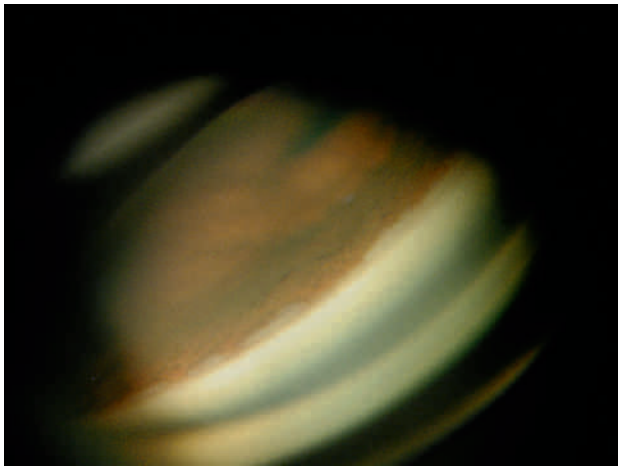

Figure 4. An example of peripheral anterior synechiae (PAS) with the iris attached to Schwalbe's line Photo: Dr Liu

Are you missing angle closure?

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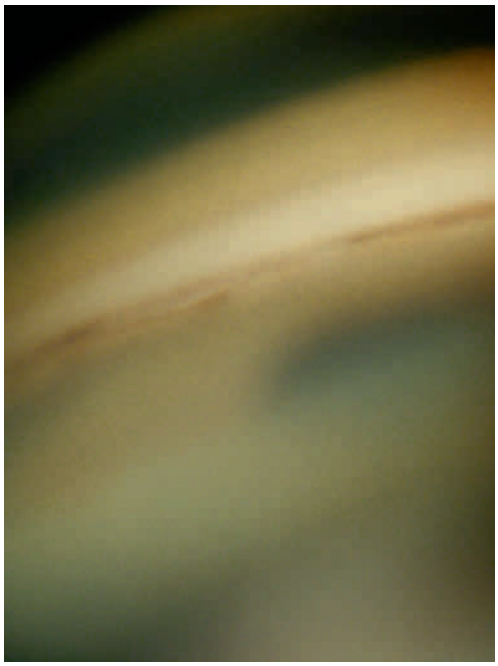

Figure 5. An example of patchy pigmentation of the trabecular meshwork due to iridotrabecular contact caused by appositional closure Photo: Dr Liu

Primary angle closure suspect: RISK
Normal optic disc
Normal IOP
ITC
Primary angle closure: DAMAGE
Normal optic disc
Raised IOP
ITC/PAS/patchy pigmentation of trabecular meshwork
Symptoms or signs of raised IOP
Includes acute primary angle closure
Primary angle closure glaucoma: DISEASE
Glaucomatous optic disc ± nerve fibre layer changes ± visual field defect(s)
Signs of primary angle closure
ITC = iridotrabecular contact

Table 1. ISGEO classification of primary angle closure glaucoma

Demographic risk factors
Increasing age
Females greater than males
Family history of glaucoma
Anatomical risk factors
Smaller anterior chamber depth
Smaller axial length
Larger lens thickness
Smaller corneal curvature
Age related hypermetropia

Table 2. Risk factors for developing primary angle closure glaucoma

- Then look for signs of appositional closure such as a high iris plane relative to the TM. There may be signs of ITC caused by appositional closure such as patchy pigmentation of the TM (Figure 5) and surrounding structures. If the pigmented TM is not visible, the central cornea can be indented with the goniolens (dynamic gonioscopy) to identify the scleral spur and to distinguish between synechial and appositional closure.
- If appositional closure is suspected, it can be confirmed by reassessing the angle in the dark. In a completely dark room, examine the angle looking for closure or ITC with a 1 mm by 1 mm slitlamp beam, taking care not to shine any light into the pupil.

If the diagnosis is unclear, the angle can be assessed with imaging technologies such as ultrasound biomicroscopy or optical coherence tomography (OCT). Appositional closure is more commonly detected and documented with OCT than with gonioscopy.[10]

Once the diagnosis of angle closure or ITC has been made, its treatment depends on the stage of treatment the patient has reached. Here, the previous classification of PACG based on symptoms (latent, intermittent, acute, chronic) is not useful as it implies the presence of glaucoma at all stages of the disease. Based on the natural history of PACG, the ISGEO classification[11] of PACG (Table 1) is increasingly being adopted, not only epidemiologically but clinically. It is divided into those who:

- are at risk of angle closure
- then develop angle damage from ITC (that is, raised IOP)
- subsequently progress to the disease or characteristic glaucomatous optic neuropathy.

As ITC can cause a rise in IOP, the natural history of this problem is that 22 per cent of PACS[12] will develop PAC while 28 per cent of patients with PAC will develop PACG.[13] ITC is more commonly found in patients with demographic and anatomical risk factors for angle closure (Table 2), which applies to all ethnic backgrounds of PACG patients.[14] Treatment in PACG is aimed at lowering the IOP and then stabilising the eye pressure (by abolishing ITC), which can be achieved medically, with laser or surgically.

Although a laser iridotomy is the first line treatment in this disease, the cause of ITC usually has a multi-mechanism aetiology. This consists of pupil block, lens induced and plateau iris mechanisms. Thus, there are non-pupil block causes that can still cause residual ITC[15] (Figures 6A and 6B), which can be treated with pilocarpine, laser peripheral iridoplasty and/or cataract surgery. It is important to repeat the gonioscopy, looking for residual angle closure or ITC.

We know that glaucoma is usually an asymptomatic disease and patients usually present when there is visual loss from the glaucomatous damage or symptoms of high IOP. In patients with primary angle closure disease, symptoms can occur in about 30 per cent of cases ranging from subtle to severe (for example,aches, pains or headaches; not clear, hazy or blurred vision; haloes, rainbows). At the extreme end of the spectrum is the clinical entity acute angle closure glaucoma, now termed acute primary angle closure (cf ISGEO classification). This condition is a medical emergency

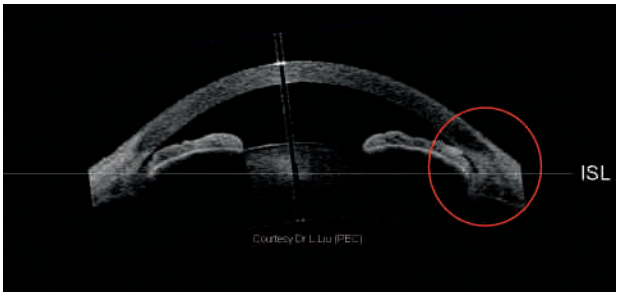

Figure 6A. Iridotrabecular contact seen in a physiologic dilated pupil in the dark

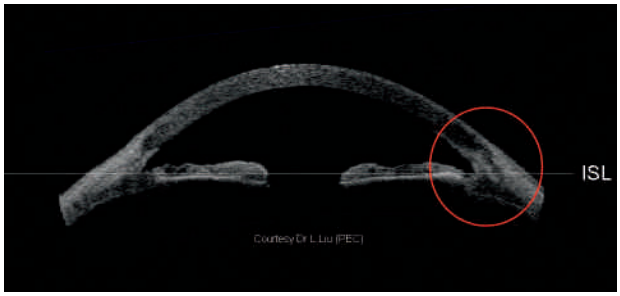

Figure 6B. Iridotrabecular contact is abolished following cataract surgery

Pharmacologic agents	Medications (generic)
Beta-blocker	Timolol/Betoptic
Alpha-agonist	Brimonidine/Apraclonidine
Carbonic anhydrase inhibitor (topical)	Brinzoladmide/Dorzolamide
Carbonic anhydrase inhibitor (oral)	Acetazolamide
Cholinergic	Pilocarpine

Table 3. Medications used in acute primary angle closure (glaucoma)

where there is a sudden rise in IOP causing a red eye, headache, nausea, vomiting and sudden loss of vision. Treatment involves lowering the IOP, either medically or treating ITC with a laser iridotomy or iridoplasty. Sometimes, indentation of the central cornea with a four mirror goniolens or with digital pressure through eyelid may also break the attack. Depending on whether the patient has any contraindications, the following IOP lowering medications should be considered in the acute situation (Table 3), with the exception of pilocarpine.

The action of pilocarpine is dependent on a functioning iris. If the pupil is fixed and dilated, it probably is ischaemic and unlikely to respond; however, if the pupil is still mobile (by checking for pupil constriction with a light source), Pilocarpine should be used. The patient should then be referred immediately to your local ophthalmologist or eye hospital for further management.

Although less common than POAG, PACG is a more blinding disease.[16] Detection and treatment, especially in its earlier stages (PACS and PAC) can alter its natural history; however, further studies are needed in this area. Therefore, gonioscopy should be performed to assess whether the angle is closed in order to determine the clinical type of glaucoma or whether the patient is at risk of developing PACG. Like visual acuity and IOP, it should be performed in all patients regardless of their presenting complaint and should be repeated yearly as angles can close over time.

We are all aware that primary angle closure disease exists but there are numerous reasons for it being underdiagnosed. The main problem is our ability to detect it as more mistakes are made by not examining with a goniolens (properly) than not knowing about angle closure.

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The ganglion cell

A new diagnostic parameter

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Spectral-domain optical coherence tomography allows measurements of macular thickness that may have a complementary role in glaucoma diagnosis.

The measurement of the perifoveal ganglion cell layer recently emerged as a new diagnostic parameter in glaucoma. Various manufacturers of spectral-domain optical coherence tomography (SD-OCT) systems have released or will soon release software upgrades capable of measuring the thickness of the ganglion cell layer. The aims of this article are to introduce the technology and speculate on its future role in glaucoma management.

Macular imaging for glaucoma

Current imaging technologies for diagnosing and evaluating glaucoma rely on measurements of the optic nerve and peripapillary retina. SD-OCT has been shown to be a useful tool in this regard.[1] Zeimer and colleagues[2] first suggested that because a significant portion of retinal ganglion cells (RGCs) reside in the macula, a loss of tissue in this region might be a sign of glaucomatous damage. This proposal was based on prior animal studies in which primate models of glaucoma demonstrated a substantial loss of RGCs in the perifoveal region.[3]

To further elucidate the relationship between macular thickness and glaucomatous damage, Lederer and colleagues[4] performed a case-controlled study evaluating macular volume, as measured by time-domain optical coherence tomography (TD-OCT), in normal and glaucomatous eyes. The study group included 70 control eyes, 70 eyes classified as glaucoma suspect, 70 eyes with early glaucoma, and 62 eyes with advanced glaucoma. Macular volume in normal (2.37 + 0.11 mm^3), glaucoma-suspect (2.33 + 0.16 mm^3) and early-glaucoma (2.27 + 0.13 mm^3) eyes was significantly greater than in eyes with advanced glaucoma (2.12 + 0.23 mm^3; P = 0.0001, P = 0.0001, and P = 0.0008, respectively).

In a separate study, Greenfield and colleagues[5] demonstrated a correlation between macular thickness measured with TD-OCT and visual field mean deviation (R2 = 0.47; P < 0.001) in 30 glaucomatous eyes. Mean macular thickness in the hemifield associated with the field defect was found to be significantly lower compared with the unaffected hemifield, further supporting a structure-function relationship. Results of these studies confirm the potential role of macular imaging in glaucoma's diagnosis and evaluation.

Macular thickness measurements were also found to correlate with peripapillary retinal nerve fibre layer (RNFL) measurements by TD-OCT in a study by Wollstein and colleagues.[6] Peripapillary RNFL thickness measurements had a higher sensitivity and specificity (area under receiver operating curve [AROC] = 0.79) for the detection of glaucomatous visual field abnormalities than the measurements of macular thickness (AROC = 0.63). In light of these results, the investigators recommended against the routine use of TD-OCT macular-thickness measurements alone in the evaluation of glaucoma.

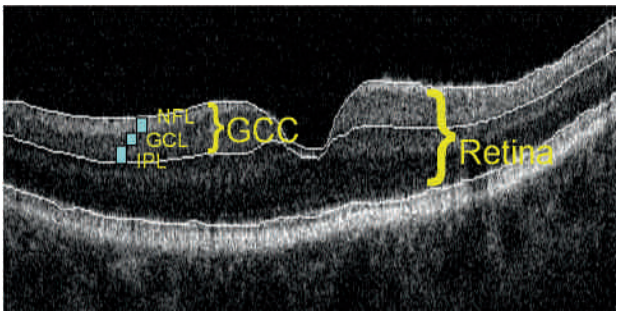

Figure 1. A cross-sectional B-scan from the RTVue in the macula region. The segmentation of the ganglion cell layer on the RTVue comprises the NFL, GCL and IPL compared to the segmentation of the entire retina.

What is the ganglion cell complex?

The ganglion cell complex (GCC) is defined* as the three innermost retinal layers: the nerve fibre layer, the ganglion cell layer and the inner plexiform layer.[7] Tan and colleagues[7] suggested that glaucoma was likely to preferentially affect these layers, rather than all macular layers, because they contain the axons, cell bodies and dendrites of ganglion cells. This idea is supported by research findings that photoreceptors do not seem to be lost in glaucoma.[8]

complex

The advent of SD-OCT has allowed for increased axial image resolution compared to TD-OCT.[9] Greater resolution now allows for the discrete segmentation and thickness measurement of the perifoveal GCC.

Diagnostic accuracy and reproducibility

Tan and colleagues[7] investigated the diagnostic accuracy and reproducibility of novel GCC parameters as measured by the RTVue FD-OCT system compared with the standard peripapillary RNFL thickness measurements obtained with TD-OCT (Stratus OCT; Carl Zeiss Meditec, Inc). In this cross-sectional study, the researchers employed existing data from patients enrolled in the Advanced Imaging for Glaucoma Study. Participants were categorised into three groups: normal (65 eyes), perimetric glaucoma (78 eyes) and preperimetric glaucoma (52 eyes). Each eye underwent scanning with the RTVue FD-OCT system for GCC analysis as well as scanning with the Stratus TD-OCT system for peripapillary RNFL analysis. AROC was then used to compare the diagnostic power of the GCC and RNFL parameters. The coefficient of variation was used to assess the reproducibility of GCC parameters.

In this study, the AROC for the three GCC parameters (overall average thickness, focal loss volume and global loss volume) were 0.90, 0.92 and 0.92, respectively. These values did not differ significantly from the AROC for average RNFL thickness (0.92; $P > 0.1$) as measured by TD-OCT in the diagnosis of perimetric glaucoma. The AROCs for GCC and RNFL parameters also did not differ for the diagnosis of preperimetric glaucoma. With regard to reproducibility, the GCC parameters outperformed (smaller coefficients of variation) RNFL parameters in normal ($P = 0.0002$) and perimetric glaucomatous ($P < 0.001$) eyes but not preperimetric glaucomatous ($P = 0.11$) eyes.

The results of this study indicate that, although GCC and average RNFL parameters perform similarly in terms of glaucoma diagnosis, the former are more reproducible and therefore may better detect glaucomatous progression.

Limitations

The limitations of SD-OCT imaging of the optic nerve head and peripapillary RNFL also apply to imaging of the GCC. Specifically, GCC analysis may be limited by signal quality,[10] image artifact,[11] and errors in the software algorithm.[12] In addition, because the GCC is imaged in the perifoveal region, any coexisting macular pathology—for example, age-related macular degeneration, macular oedema, epiretinal membrane—may affect GCC thickness measurements.

Imaging of the perifoveal GCC limits analysis to ganglion cells associated with the central visual field. In early glaucoma, visual field defects and corresponding damage to the ganglion cells may occur far from fixation and therefore escape detection when imaging only the perifoveal GCC.

Future directions

In their study comparing GCC parameters with standard RNFL parameters, Tan and

Continued page 12

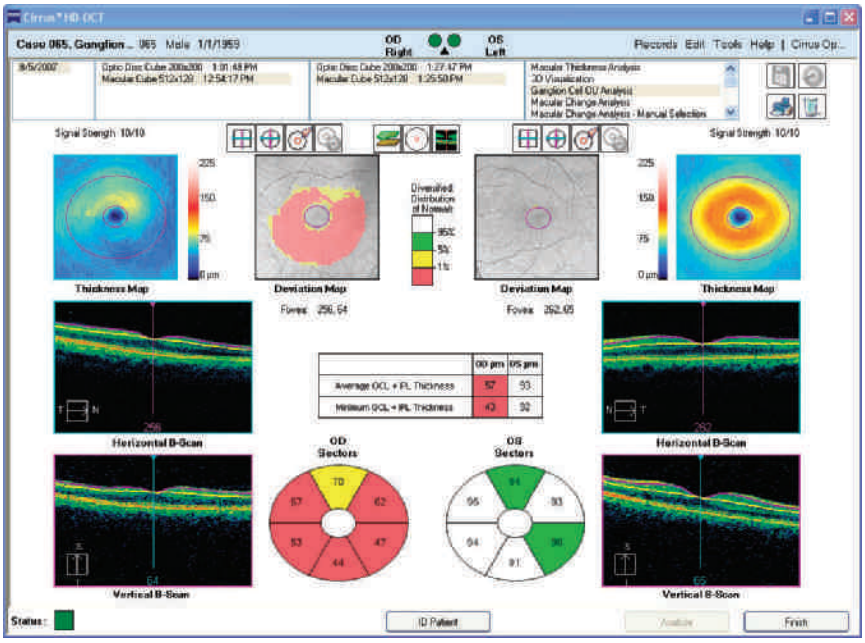

Figure 2. Carl Zeiss's Cirrus HD-OCT ganglion cell OU analysis screen, containing:

- **Thickness map showing thickness measurements of the GCL + IPL in the 6 mm by 6 mm cube, contains an elliptical annulus centred about the fovea**
- **Deviation map showing a comparison of GCL + IPL thickness to normative data (red to indicate where thinner than all but one per cent of normals, yellow to indicate thinner than all but five per cent of normals**
- **Thickness table showing average and minimum thickness within the elliptical annulus**
- **The Sectors in the lower portion of the screen divide the elliptical annulus of the thickness map into six regions: three equally-sized sectors in the superior region and three equally-sized sectors in the inferior region**
- **Horizontal and Vertical B-scans: the slice navigator in the Vertical B-Scan is used to adjust to a different Horizontal B-Scan and vice versa**

Ganglion cell complex

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colleagues[7] also found that combining the two parameters significantly increased the detection rate of both preperimetric and perimetric glaucoma. Newer software algorithms will be likely to combine RNFL, optic nerve head and GCC parameters to further increase the diagnostic yield of SD-OCT and will also lead to better reproducibility for accurate tracking of glaucomatous progression. Further investigation of the GCC is likely to lead to the standardisation of current software algorithms and their availability across all manufacturers of SD-OCT technology.

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Addendum

Since the initial publication of this article, Dr Aref has provided *Pharma* with the following update.

To date, three OCT manufacturers have FDA-approved software algorithms looking at macular thickness for glaucoma diagnostics: Carl Zeiss, Optovue and Heidelberg Engineering. Each of the different software algorithms measures a different aspect of the macula. The Carl Zeiss protocol (Ganglion Cell Analysis, GCA) measures only ganglion cell layer and inner plexiform layer thicknesses. The Optovue protocol (Ganglion Cell Complex, GCC) measures the retinal nerve fibre layer, ganglion cell layer and inner plexiform layer thicknesses. The Heidelberg protocol (Asymmetry Analysis) measures the entire macular thickness. All of these software algorithms are proposed to aid in the diagnosis of glaucoma but are yet to be compared with each other.

New software algorithms combining retinal nerve fibre layer, optic nerve head and ganglion cell complex parameters have not yet been developed. To my knowledge, there have not been any new studies looking at GCC parameters and glaucomatous progression.

* The definition of 'ganglion cell complex' differs among manufacturers. Optovue defines it as the retinal nerve fibre layer (RNFL), the ganglion cell layer (GCL) and the inner plexiform layer (IPL). Carl Zeiss defines the ganglion cell complex as a combination of the GCL and the IPL—excluding the RNFL. Heidelberg's asymmetry analysis measures the entire macular thickness.

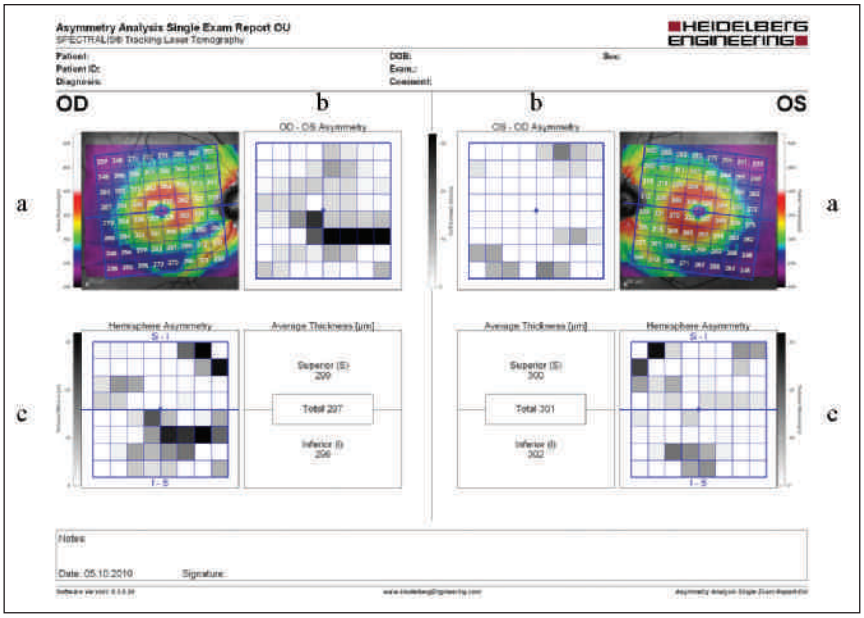

Figure 3. Heidelberg Spectralis asymmetry analysis retinal thickness map displays the retina thickness over the entire posterior pole for each eye. Mean retinal thickness in each cell of the 8 x 8 grid in one eye is compared to the thickness in the corresponding cell of the fellow eye. Hemisphere asymmetry displays the asymmetry between the superior and inferior hemisphere. The fovea-disc axis is the horizontal symmetry line. For each cell of one hemisphere, the mean retina thickness is compared to the value in the corresponding cell for the opposite hemisphere.

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Guided progression analysis

A tool in assessing risk of future vision loss

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Detecting glaucoma progression on a perimeter is a tricky business. First, the clinician must decide whether any change is due to disease progression or from inconsistent performance by the patient or whether it is simply normal variation between tests. Second, if the change is due to progression in a condition, is it due to glaucoma or is it simply something else such as advancing cataract?

This is why guided progression analysis (GPA) was developed for the Humphrey Field Analyzer. GPA aims to achieve three things: distinguish statistically significant visual field progression from normal test-retest variability, filter out the effects of advancing cataract and measure the rate of disease progression. It does so by using event analysis (is there statistically significant change from baseline?) as well as trend analysis (what is the rate of change?).

Event analysis

One of the biggest problems with detecting glaucoma progression using perimetry is determining whether any perceived change is due to disease progression or normal variability. It is important to recognise that every clinical test has certain test-retest variability, whether it is testing visual acuity, tonometry or simply measuring IPD with a ruler. No test gets exactly the same result every time. For perimetry, the variability is even greater due to the subjective nature of the test. To determine real change from normal variability, we have to define what the expected test-retest variability actually is.

To solve this problem, the developers of GPA conducted visual field testing on 363 glaucoma patients in 16 centres over three continents, with diseases ranging from early to advanced stages. Each subject attended the clinic four times in the period of one month and underwent three visual field tests each time: one using Swedish Interactive Threshold Algorithm (SITA) Standard, one using SITA Fast and one using Full Threshold programs.

In well-managed patients, one month is not long enough for glaucoma to progress; however, four tests is enough to measure fluctuations from visit to visit and therefore define the expected test-retest variability of glaucoma patients. Additionally, the three testing strategies were used so that GPA could be applied to all of these strategies, no matter which one is being used. What was developed was not a normative database but a database that defines the corridor of normal test-retest variability in glaucoma patients spanning the range from early to advanced disease.

If GPA detects a test point that has deteriorated by more than test-retest variability seen in 95 per cent of patients, it is flagged using one of three triangular symbols. An open triangle denotes significant progression from baseline on the current test only, a half-filled triangle denotes significant progression in two consecutive examinations from baseline and a fully-filled-in triangle denotes significant progression from baseline in three consecutive examinations (Table 1).

Continued page 14

△	**Small open triangle**: identifies any test point that has worsened by an amount that exceeds the variability expected in all but the most variable five per cent of glaucoma patients having similar visual field status ($p < 0.05$). This symbol is used when the change was not seen on the previous follow-up test.
◭	**Half-filled triangle**: identifies a point changing by an amount that is significant at the $p < 0.05$ level and that is repeated in two consecutive follow-up examinations
▲	**Filled triangle**: identifies a point changing by an amount that is significant at the $p < 0.05$ level and that is repeated in three consecutive follow-up examinations

Table 1. The GPA progression indicator symbols

Guided progression analysis

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If there are three or more half-filled triangles on a test, GPA labels it 'possible progression'. If there are three or more fully-filled triangles, GPA labels it 'likely progression'. These plain-language progression alerts are very useful for interpretation, especially since they use the same validated progression criteria as used in the Early Manifest Glaucoma Trial, a well-regarded longitudinal study that followed 255 glaucoma patients over six years.[1,2]

It is important to note that GPA never proclaims 'definite progression' because this is the job of the clinician considering all available clinical information.

Three important things must be noted regarding the variability measured in this data set. Significantly, it was found that test-retest variability is different depending on test location, defect depth and level of mean deviation—in other words, how much, on average, the whole field departs from normal.

First, peripheral points vary more than central points and second, more depressed points vary more than normal points from test to test. Interestingly, test points in a visual field with a poor mean deviation (MD) vary more than points having the identical defect depth in a field with a relatively normal MD.

Keeping this in mind, these findings were built into the progression criteria of GPA so that a more depressed, peripheral test point must progress by more to be flagged as significant compared to a normal, more central test point (Figure 1). The same is true for points in a field with a poor MD compared to those on a visual field with normal MD.

Minimise false positives

Whenever one does a test repeatedly, statistically speaking there is always a chance of a false positive result, indicating disease progression where there is none. This must be controlled for in the test design, especially since GPA can track change over 14 tests. GPA controls for this at the start and one at the end of the test series. At the start, the baseline is calculated on the average of two examinations, thus minimising the risk that GPA is basing change on a single outlier. At the end, GPA requires significant change from baseline to be maintained in three consecutive examinations, thereby confirming the result three times. These two strategies were used in the Early Manifest Glaucoma Trial and found to have excellent specificity—they effectively minimised the possibility that the detected change was a false positive.[1]

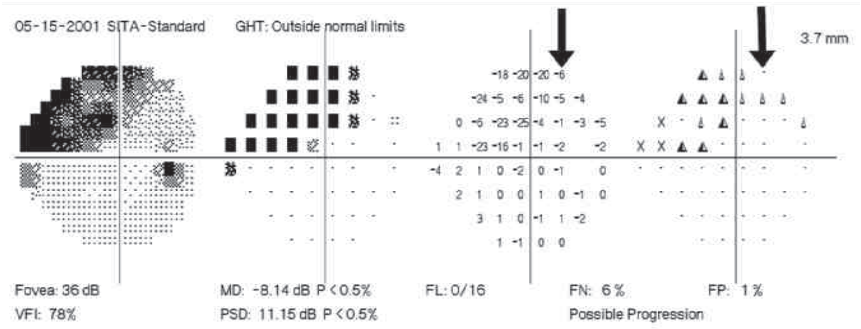

Figure 1. In this example, GPA has identified a peripheral superior point that has progressed by 6 dB as not significant, whereas adjacent points of only 4 dB and 5 dB progression are indentified as significant due to the fact that they are more central

Trend analysis

By using the triangular probability symbols, GPA shows whether statistically significant change has occurred. This is important but it does not tell us the rate of change.

In the past, measuring rate of change has been problematic due to the fact that it could be based only on traditional indices such as mean deviation. The problem is that these indices are sensitive to both glaucoma progression as well as the effect of cataract; therefore, a lowering of MD could mean worsening glaucoma or advancing cataract or both. Similarly, indices such as MD will increase after cataract surgery, further confounding the results.

Heijl and Bengtsson, who developed the GPA in Sweden, developed a new index called the visual field index (VFI), which has a number of important features.

- It is expressed in an intuitive percentage scale: 100 per cent being a full field and zero per cent being perimetric blindness.
- The VFI is based on the Pattern Deviation Probability Plot, which compensates for changes in the hill of vision caused by factors such as cataracts and pupil size.
- The VFI is weighted more centrally than peripherally to reflect the greater concentration of ganglion cells in the central field, therefore improving the correlation between structure and function. This weighting also has the side benefit of recognising the greater importance of the central and paracentral points compared to the peripheral points. Thus, Heijl and Bengtsson developed an index specifically designed for rate of change analysis and their published results show that VFI is considerably more resistant

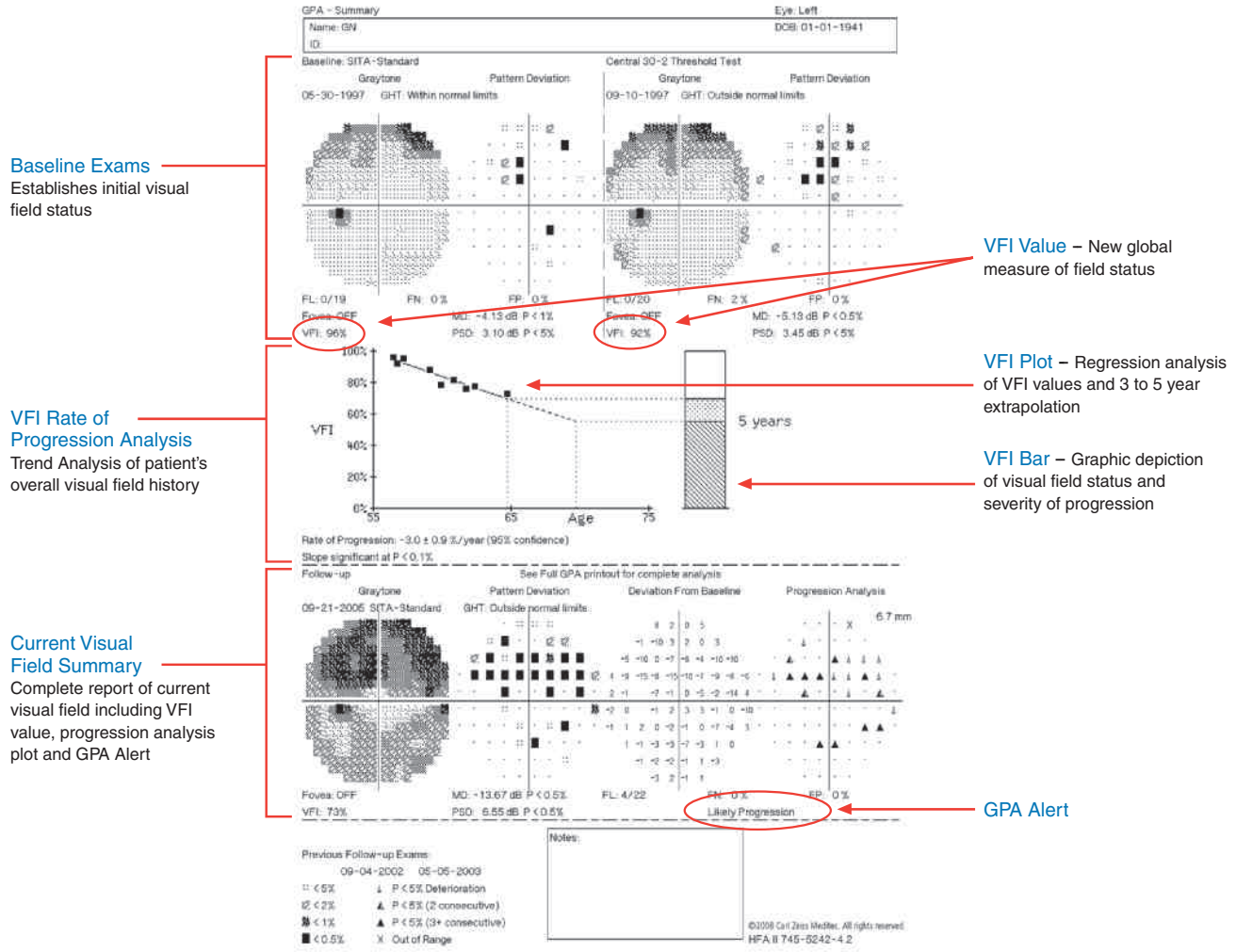

Figure 2. How to interpret the GPA summary report

than traditional MD to changes due to cataract.[3] An additional benefit is that the index is easily understood by patients.

Once there are five tests over at least two years, GPA conducts a linear regression analysis to establish the rate of change in VFI per year. This regression line is projected up to five years into the future, to indicate how the patient may change if the current rate of progression is not altered. This technique has been published in the literature and found to be a reliable predictor of future visual field loss in most patients;[4] therefore, it can be helpful not only in treatment decisions but also for patient education.

GPA reveals not only statistically significant change beyond that of expected test-retest variability but also the rate of change while controlling for cataract. Both pieces of information are invaluable for a clinician managing glaucoma and are designed to help with important treatment decisions.

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Device mimics eye's hydraulics

A surgical device being developed at the Centre for Eye Research Australia could reduce the number of glaucoma operations.

Principal investigator Dr Michael Coote said the device, made from a porous polymer material, will resemble a tube and could be fitted into a sealed pocket under the eye lid during surgery.

The device will help to maintain safe levels of fluid in the eye to help limit post-operative scarring and reduce the need for future surgery.

'We aim to develop a device that mirrors the eye's natural hydraulics,' Dr Coote said.

It is being developed in conjunction with the Royal Victorian Ear and Eye Hospital and is expected to undergo human trials at the end of 2012.

Risk higher in US southern states

Age, gender and place of residence could affect a person's risk of developing secondary open-angle glaucoma.

According to a United States study, researchers used data from two studies, the Nurses' Health Study and the Health Professionals Follow-up Study, to evaluate the descriptive epidemiologic features of exfoliation syndrome, a leading cause of secondary open-angle glaucoma.

Of the 78,955 women and 41,191 men surveyed, researchers found that those living in the middle and southern regions of the United States had 47 per cent and 75 per cent reduced risks, respectively, compared to their northern region counterparts.

The data also suggested that there was an increased risk in females, and a positive family history of glaucoma was associated with a more than two-fold increase in risk.

Ophthalmology 2012; 119: 1: 27-35.

Abstracts

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High prevalence of ocular surface disease in patients with glaucoma

Patients who use topical intraocular pressure (IOP)-lowering therapies have been shown to have a high prevalence of ocular surface disease.

In this multi-centre, non-interventional study, adults with glaucoma or ocular hypertension (n = 488; mean age 63.0 years) who were using more than one topical IOP-lowering medication completed the Ocular Surface Disease Index (OSDI) questionnaire during a scheduled clinic visit. OSDI scores (ranging from 0-100) were calculated; an OSDI ≥ 13 indicates clinically-relevant ocular surface disease.

The prevalence of significant ocular surface disease in the evaluated population was 59.2 per cent. Patients with glaucoma diagnoses of less than six years had a significantly lower OSDI (mean ± SD: 18 ± 16) relative to patients with glaucoma diagnoses in excess of six years (mean ± SD: 23 ± 21; p = 0.03).

The authors concluded that consideration with regard to treatment of anterior eye signs and symptoms should be considered in patients with glaucoma, particularly those with long-standing disease or who use multiple topical preparations.

Clin Ophthalmol 2012; 6: 441-446.

Corneal-thickness and long-term outcome of laser trabeculoplasty

The degree of intraocular pressure (IOP) reduction after selective laser trabeculoplasty (SLT) for the management of primary open angle glaucoma (POAG) and ocular hypertension (OHT) has been found to be significantly greater in eyes with thinner corneas (central corneal-thickness [CCT] < 555 µm).

A retrospective chart review of consecutive patients at the Department of Ophthalmology, Massachusetts Eye and Ear Infirmary (Harvard, Boston, MA), who underwent SLT as primary treatment for OHT or POAG (2002-2005) was performed. Partial correlation analysis was undertaken to correlate CCT to the percentage IOP-reduction at three to 30 months post-SLT.

Eighty eyes of 47 patients were identified (age, mean ± SD: 66.5 ± 10.1 years). Independent sample t-tests indicated that the mean per cent IOP reduction in eyes with thinner corneas (that is, CCT 555 µm) was greater than that in thicker corneas (CCT > 555 µm) at three, six, nine, 12 and 30 months post-SLT ($p < 0.05$). The percentage difference (mean ± SD) in IOP-reduction from baseline was 29.0 ± 12 per cent in the thin cornea group versus 22.7 ± 11.4 per cent in the thick cornea group ($P < 0.05$) at 30 months post-SLT.

These findings suggest that patients with relatively thinner CCTs may experience more significant long-term reductions in IOP from SLT.

Cornea 2012; Apr 19 (Epub ahead of print).

Optometrists and specialists agree on management of patients

Data from a study conducted in the Manchester Royal Eye Hospital (UK), to assess the agreement between specially trained optometrists and glaucoma-specialist ophthalmologists in their management of glaucoma patients, has confirmed the ability of optometrists to make appropriate decisions regarding the stability and management of these patients.

Optometrists (n = 4) examined about 23 or 25 patients each and documented their clinical findings. The optometrist and one of two consultant ophthalmologists independently examined the optic disc appearance, visual fields (VFs) and intraocular pressures (IOPs) before recording a decision with regard to the stability and management of the patient.

Agreement between consultants and optometrists in evaluating glaucoma stability was 68.5 per cent ($\kappa = 0.42$-0.50) for VFs, 64.5 per cent (weighted $\kappa = 0.714$-0.31) for optic discs and 84.5 per cent (weighted $\kappa = 0.55$-0.60) for IOPs. Agreement regarding medical management was 96.5 per cent ($\kappa = 0.73$-0.81) and for other glaucoma management decisions, including timing of follow-up, referral, discharge, was 72 per cent (weighted $\kappa = 0.65$).

Eye (Lond) 2012; Apr 13 (Epub ahead of print).

Do patients with glaucoma have difficulty recognising faces?

Patients with advanced glaucoma have been found to experience problems with face recognition compared with age-matched controls.

Face recognition performance was compared between patients with established glaucoma of varying severity (n = 54, mean age: 69 years) and visually-healthy controls (n = 41, mean age: 67 years). All participants underwent cognitive and visual assessment–visual acuity, contrast sensitivity (CS) and Humphrey visual field (VF) analyses, 10-2 and 24-2 thresholds. Glaucoma severity was classified as early, moderate or advanced using the VF criteria defined by Hodapp, Parrish and Anderson.

Glaucoma patients with advanced VF deficits identified fewer faces (mean ± SD: 66 ± 15 per cent, $p < 0.05$) than those with early (75 ± 11 per cent) or moderate (75 ± 13 per cent) VF defects, or controls (75 ± 11 per cent).

Overall, when compared to age-matched normals, glaucomatous patients with advanced bilateral VF loss on 24-2, significant ($p <$ one per cent) losses on the 10-2 VF or poor contrast sensitivity were most likely to experience difficulties with face recognition.

Invest Ophthalmol Vis Sci 2012; Apr 17 (Epub ahead of print).

Nutrient intake and risk of open-angle glaucoma: the Rotterdam Study

A low dietary intake of retinol equivalents, vitamin B1 and a higher intake of magnesium have been shown to be associated with an increased risk of open-angle glaucoma (OAG).

A prospective, population-based cohort study, the Rotterdam Study, was conducted involving 3,502 participants aged ≥ 55 years who did not have glaucoma at baseline. The dietary intake of nutrients having either anti-oxidative properties (carotenoids, vitamins and flavenoids) or vaso-active effects (omega fatty acids and magnesium) were assessed relative to incident glaucoma. Ophthalmic examinations consisted of intraocular pressure and perimetry. Dietary intake of nutrients was assessed by a validated questionnaire and adjusted for energy intake.

During an average follow-up of 9.7 years, 91 participants (2.6 per cent) developed OAG. The hazard ratio for retinol equivalents (highest versus lowest tertile) was 0.45 (95% CI: 0.23-0.90), for vitamin B1 was 0.50 (0.25-0.98) and for magnesium was 2.25 (1.16-4.38).

Eur J Epidemiol 2012; Mar 30 (Epub ahead of print).

Adherence to glaucoma medication is associated with personality type

Poor adherence to topical glaucoma medications regimes has been shown to be associated with certain personality types.

Glaucoma patients using prostaglandin monotherapy were prospectively randomised to an intervention (n = 38) or non-intervention (n = 42) group. Over five months, the intervention group received monthly automated telephone calls reminding them to instil their eye-drops; at month three, this group underwent ophthalmologic examination and received education regarding their disease and treatment.

The non-intervention group returned at the end of the study. Adherence was directly measured with an electronic monitoring cap. Patients also completed the Minnesota Multiphasic Personality Inventory-2.

Over five months, the mean adherence rate for the intervention group over five months was 76 per cent versus 80 per cent for the non-intervention group ($p > 0.05$). Ophthalmologic intervention (phone calls and in-office visit) did not improve the adherence rate with glaucoma medications but depression and hypochondriasis personality types were consistently associated with poor adherence. These findings highlight the role of psychosocial factors in medication adherence.

J Glaucoma 2012; Mar 8 (Epub ahead of print).

Risk factors in ocular hypertension and primary open angle glaucoma

This exploratory, case-controlled study evaluated potential risk factors–nutrition, lifestyle and environment–differentiating patients with primary open angle glaucoma (POAG) from control subjects with ocular hypertension (OHT).

From 2006-2007, French ophthalmologists (n = 111) enrolled cases of POAG (n = 339) and age-matched controls with OHT (n = 339). Following a clinical examination with assessment of ocular risk factors, a detailed questionnaire was completed on lifestyle and environmental risk factors, including socio-demographic variables, dietary habits, smoking, alcohol intake and professional exposure to pesticides and other chemicals.

POAG was found to be significantly associated with more frequent use of pesticides during professional life (Odds Ratio, OR = 2.65, 95% CI: 1.04-6.78, p = 0.04) and low consumption of fatty fish (OR = 2.14, 95% CI: 1.10-4.17, p = 0.02), and walnuts (OR = 2.02, 95% CI: 1.18-3.47, p = 0.01). POAG was also associated with higher frequency of heavy smoking (OR = 3.93, 95% CI: 1.12-13.80. p = 0.03).

It was concluded that these observations suggest a protective effect of omega-3 fatty acids and a deleterious effect of heavy smoking and professional exposure to pesticides in the development of POAG.

Acta Ophthalmol 2012; Mar 6 (Epub ahead of print).

Impaired ocular blood flow regulation in patients with POAG and diabetes

Diabetes may interfere with normal vascular regulation and contribute to glaucoma progression.

A cross-sectional analysis was performed from a longitudinal, prospective study. A total of 84 POAG patients (n = 20 with co-existent diabetes, n = 64 without diabetes) were analysed for optic nerve morphology, peri-papillary retinal nerve fibre layer (RNFL) thickness, ocular perfusion pressure (OPP), retrobulbar blood flow and retinal capillary perfusion.

Central-retinal artery (CRA) peak systolic velocity was 13.5 per cent lower in diabetic patients (p = 0.007). In diabetic POAG patients, negative correlations were found between retrobulbar and retinal circulations; whereas positive correlations between retinal flow and non-flow were only observed in non-diabetic POAG patients.

Impaired ocular blood flow regulation with patients with POAG and diabetes was hypothesised to contribute to glaucoma progression in this patient demographic.

Clin Experiment Ophthalmol 2012; Mar 7 (Epub ahead of print). ■

Boosting mitochondria

A new approach for protecting aged optic nerve in glaucoma

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Glaucoma, ageing and mitochondrial dysfunction

Population studies have shown that ageing is a major risk factor for glaucoma, with prevalence and incidence rising near exponentially with advancing age.[1] Due to ageing of the population, the number of individuals affected by glaucoma is set to double in the next 25 years, posing a major challenge to future health-care provision as life expectancy continues to increase.

The core pathophysiology underlying glaucoma is accelerated degeneration of retinal ganglion cells and their axons. While the mechanisms by which ageing predisposes aged retinal ganglion cells to glaucomatous degeneration are unclear, increasing evidence implicates mitochondria. Accumulation of somatic mitochondrial DNA mutations and impaired mitochondrial respiration is seen with advancing age[2] and has been shown to act causally in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.[3]

Due to their high rates of metabolism, retinal ganglion cells contain high numbers of mitochondria that are concentrated along unmyelinated axons (Figure 1). Retinal ganglion cells are specifically sensitive to mitochondrial abnormalities, as evidenced by the optic neuropathies Leber's hereditary optic neuropathy and autosomal dominant optic atrophy, both of which are caused by mitochondria-related genetic defects and result in the selective loss of retinal ganglion cells.

Associations between mitochondrial dysfunction and glaucoma are now emerging. Increased mitochondrial DNA mutations, leading to an overall decline in respiratory activity, has been reported in patients with primary open-angle glaucoma (POAG).[4] We have published additional evidence of reduced mitochondrial-driven ATP synthesis together with impaired respiration in lymphoblasts of POAG patients compared to age-matched controls.[5]

Given these observations, we believe that mitochondrial dysfunction, and the subsequent oxidative stress and defects in cellular energy production, render aged retinal ganglion cells susceptible to glaucomatous injury (Figure 2). Our research focuses on understanding mitochondrial dysfunction in the ageing retina with the ultimate aim of identifying novel mitochondrial-targeted therapies for protecting the optic nerve in glaucoma.

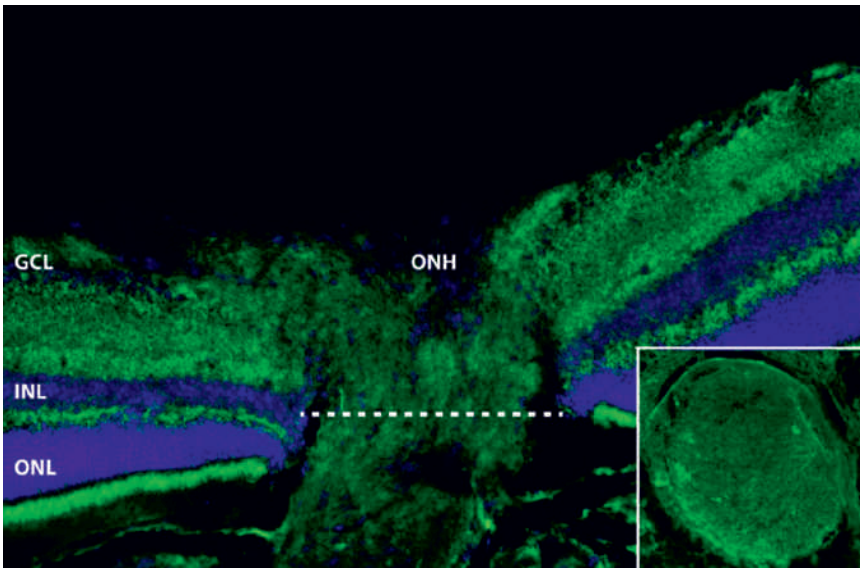

Figure 1. The proximal optic nerve head contains high concentrations of mitochondria, reflecting the high energy requirements of retinal ganglion cells, as shown by immunolabeling for the mitochondrial enzyme cytochrome c oxidase (green)

Diet restriction

Diet restriction, both through a reduction in total caloric intake or alternate-day fasting, prolongs life and reduces susceptibility to age-related chronic diseases including cancer, atherosclerosis and diabetes.[6,7] It has also been shown that diet restriction is neuroprotective in experimental rodent models of Alzheimer's disease, Parkinson's disease and neuronal death induced by excitotoxins.[8] In light of these findings, orally active substances that mimic the protective effects of diet restriction such as resveratrol, a naturally occurring polyphenol that is present in red wine and certain food products, are gaining much attention.

At a cellular level, diet restriction is known to induce the formation of new mitochondria (mitochondrial biogenesis) and enhance mitochondrial function (Figure 3).[9] Our group has published evidence that diet restriction in middle-aged mice, in the form of alternate-day intermittent fasting, reverses an age-related decline in protein expression and enzymatic activity of mitochondrial oxidative phosphorylation components in the retina.[10] We show that mice subjected to intermittent fasting have significantly improved retinal ganglion cell function after pressure-induced injury compared to age-matched ad libitum-fed control animals.

Exercise

At a cellular level, it is well accepted that exercise induces structural and functional

changes to mitochondria. Many of these changes and the underlying molecular signalling pathways are similar to those seen in response to diet restriction (Figure 3). Physical activity is a potent stimulator of mitochondrial biogenesis in heart, skeletal muscle and brain, leading to enhanced mitochondrial respiration and a corresponding increase in oxygen consumption and ATP synthesis.[11,12]

At a systemic level, the benefits of exercise to general health are firmly established. Exercise prevents all-cause mortality and protects against a range of conditions such as diabetes, coronary heart disease, hypertension and several forms of cancer. There is strong evidence to suggest that exercise is neuroprotective. Physical activity has been shown to protect the brain and spinal cord under normal ageing, following injury, and in age-related neurodegenerative conditions such as Parkinson's disease and Alzheimer's disease.[13,14] As a therapy, exercise is cost-effective, non-invasive and safe.

The relationship between physical activity and ocular health is largely unexplored. Reports on the effect of exercise on retinal cell survival and function are lacking and there is little known about the role of exercise in age-related eye disease. With support from the Ophthalmic Research Institute of Australia and Glaucoma Australia, we are conducting a study that aims to characterise the impact of exercise on the aged retina and optic nerve, and test if exercise can protect the aged retina and optic nerve from injury.

We recently completed preliminary experiments in which middle-aged mice underwent six weeks of daily exercise. We found that exercised mice show significantly less retinal ganglion cell dysfunction in response to pressure-induced injury compared to age-matched control (sedentary) mice. In association with improved functional recovery, we see signs of reduced oxidative stress in injured eyes of exercised mice compared to sedentary mice. To the best of our knowledge, these data provide the first evidence that exercise can protect retinal cells from an experimental injury. We are now investigating the mechanisms underlying this protective effect.

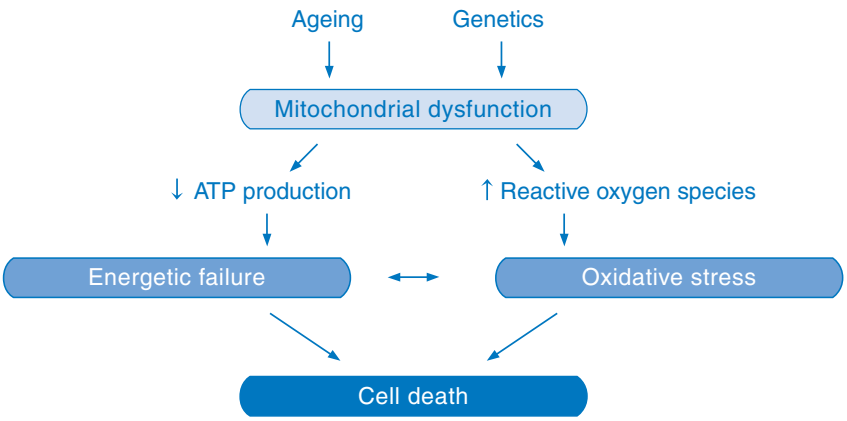

Figure 2. Potential pathways through which mitochondrial dysfunction can lead to retinal ganglion cell death

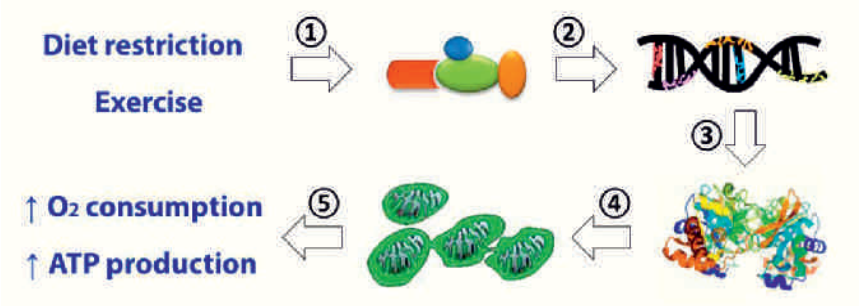

Figure 3. Cellular events proposed to be involved in promoting mitochondrial biogenesis and function in response to diet restriction and exercise

1. **Activation of transcription modulators (for example, PGC-1a, NRF-1, PPAR)**
2. **Transcription of mitochondrial genes**
3. **Synthesis of mitochondrial proteins and enzymes**
4. **Formation of new mitochondria**
5. **Enhanced mitochondrial function**

Summary

The development of neuroprotective therapies that render the optic nerve more resistant to injury and complement current glaucoma treatments that lower eye pressure are urgently needed. Therapeutic approaches that target mitochondria and promote energy production may provide a general means of protecting aged retinal ganglion cells from degeneration. Our research suggests that the impact of ageing and mitochondrial dysfunction on retinal ganglion cells can be modified by diet restriction and exercise. These findings point to the potential for novel therapies that boost mitochondrial function to protect the aged optic nerve in glaucoma.

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The need for a comprehensive test

We can find the 50 per cent of undiagnosed cases of glaucoma if a thorough history and examination come first, followed by investigations to confirm a clinical diagnosis

It's not what you look at that matters, it's what you see.
Henry David Thoreau, 1817-1862

In 1996, the Blue Mountains Eye Study (BMES) reported the prevalence of glaucoma in an Australian population-based study.[1] This was shortly followed by data from the Melbourne Visual Impairment Project (VIP) in 1998.[2] Unfortunately, both studies independently found that about 50 per cent of glaucoma was undiagnosed. Worse still, 59 per cent of the subjects had visited an eye-care provider in the previous year.[3]

Glaucoma prevalence increases exponentially with age and currently affects one in 10 Australians over the age of 80.[1,2,4] Like all First World nations, Australia will face an ageing demographic. The corollary is that there will be an increased prevalence of age-related eye diseases.

Collaborative work by the University of Melbourne's Centre for Eye Research Australia and Access Economics has reported on the economic impact of primary open angle glaucoma on Australia.[5] Their modelling predicts an 80 per cent increase in the prevalence of glaucoma by 2025. The direct health-care costs involved in the care and management of glaucoma patients are expected to increase from $355 million to $784 million. Glaucoma remains the only preventable form of age-related blindness. We, as eye-care practitioners, need to be part of the solution.

Population screening of asymptomatic persons for glaucoma has not been considered to be cost-effective.[6] Targeted screening of populations at high risk for glaucoma may be more useful but this requires a thorough patient history, followed by a comprehensive examination and only finally, tests and investigations to confirm and document our diagnosis. Too often, as clinicians we are tempted to use investigations as a lazy way to diagnose disease. This often leads to false positive or incoherent results, increased patient angst and ultimately, increased costs to the patient and community.

The recently released NHMRC Guidelines for the screening, prognosis, diagnosis, management and prevention of glaucoma, 20107 and its companion Guide to Glaucoma for Primary Health Care Providers, 20118 are excellent resources and are freely available in electronic format.

The NHMRC guidelines were developed as a tool for health-care providers and to present current best evidence for the management of glaucoma. They are not a protocol and the authors emphasise the need to individualise patient treatment and care. The document summarises key evidence statements and provides practice recommendations based on the available evidence.

To increase our effectiveness in identifying individuals with glaucoma or at risk of developing glaucoma, the NHMRC guidelines strongly recommend adopting a standard approach to assessing the known risk factors of this disease. A comprehensive glaucoma history at each of our consultations should include consideration of the patient's:

- **Age**: the prevalence of glaucoma increases 4-10 times in the older age groups
- **Family history**: individuals with a close relative with primary open angle glaucoma (POAG) are at 3-6 times greater risk of glaucoma.
- **Ethnic origin**: persons of African descent have a higher age-adjusted prevalence of POAG; and persons of Asian descent have a higher reported rate of primary angle closure glaucoma (PACG).
- **Refractive status**: population studies have identified an increased prevalence of glaucoma in myopes; there is also a high correlation between high hypermetropes and shallower anterior chambers.
- **Diabetes**: the association with POAG is controversial but individuals with diabetes should always be targeted for blindness prevention programs.
- **Systemic blood pressure**: low systemic blood pressure, in particular low diastolic blood pressure, and nocturnal hypotension are risks for reduced ocular perfusion pressure, and contribute to normal tension glaucoma (NTG) and POAG. There is a complex relationship between systemic hypertension and glaucoma.
- **Previous eye trauma**: in particular blunt injury, where angle recession is a risk factor for secondary OAG. Penetrating trauma may be associated with complex reconstructive surgery and damage to critical ocular structures.
- **Migraine and peripheral vasospasm**: have been identified as risk factors for reduced ocular perfusion and NTG or POAG.
- **Long-term steroid users**: steroids administered by any route are associated with increased risk of glaucoma. Importantly, we must also be alert to the potential of steroid-like substances from traditional and natural medicines.

The thorough clinical history should be followed by a comprehensive ocular examination that includes:

- **Intraocular pressure**

Look for elevated or fluctuating intraocular pressures. IOP is a risk factor for the devel-

	Glaucoma	No glaucoma	Total population
Test positive	450	100	550
Test negative	50	400	450
Total	500	500	1,000

Population prevalence 50 per cent, test sensitivity 90 per cent, test specificity 80 per cent

	Glaucoma	No glaucoma	Total population
Test positive	18	196	214
Test negative	2	784	786
Total	20	980	1,000

Population prevalence two per cent, test sensitivity 90 per cent, test specificity 80 per cent

opment and progression of POAG. The level of IOP that causes nerve damage varies between individuals. Clinicians should be aware that half of those with POAG do not have increased IOP, while only a certain proportion of those with elevated IOP (ocular hypertension) will develop glaucoma. Glaucoma diagnosis no longer rests solely on the IOP.

- **Gonioscopy**

Categorise angle morphology into the two major subtypes: open angle or closed angle glaucoma. Further assessment includes dynamic gonioscopy, evidence of intermittent angle closure, peripheral anterior synechiae and other congenital or acquired anomalies of the trabecular meshwork.

- **Optic disc examination**

Determine the disc colour and size, peripapillary atrophy, cup:disc ratio including asymmetry between eyes, focal neuroretinal rim thinning, nerve fibre layer defects, and optic disc haemorrhages—performed stereoscopically through dilated pupils. Serial disc photography is also clinically useful but should not be substituted for an optic disc examination

- **Corneal thickness (CCT)**

Use as a surrogate for corneal hysteresis (biomechanical rigidity). It remains a risk factor for the disease. Although corneal thickness contributes to the measurement error with our common tonometers, IOP should not be 'adjusted' for corneal thickness. This relationship between IOP and CCT is non-linear and more complex than the linear regression algorithms and tables suggest.

Finally, investigations are used to confirm, document and monitor progression once a clinical diagnosis is made. We must not fall into the trap of investigating to diagnose a disease. A scatter-gun approach to investigations leads to wasteful costs for both the patient and the community. Clinicians must understand the reason for and limitations of these investigations, and be able to make meaningful interpretations of the results.

A recent paper by Thomas and colleagues discusses the futility of testing in cases where the pre-test probability is low.[9] He describes how Bayes' theorem can be used to calculate the post-test predictive value of a positive test result. Whenever a clinician orders an investigation, what they are truly interested in is the proportion of subjects with a positive test result who have the disease, that is, the positive predictive value.

This is particularly relevant where clinical practice has increasingly moved to using investigations indiscriminately to detect disease. The statistics behind these calculations are beyond the scope of this article but interested readers are encouraged to refer to the above mentioned paper.[9]

Let us assume we have a good glaucoma test, such as OCT or HRT nerve fibre analysers, with a high sensitivity of 90 per cent (test positive and glaucoma present) and specificity of 80 per cent (test negative and glaucoma absent) of detecting disease. If we undertake this test on 1,000 persons where the population prevalence of disease is high, say 50 per cent, then the post-test positive predictive is 450/550 (82 per cent). This means that 82 per cent of subjects with a positive test result truly have the disease.

If we use the same test indiscriminately on 1,000 persons to test them for glaucoma, when the overall Australian population prevalence of glaucoma is about two per cent (prevalence ranges from 0.3 per cent at 40 years of age, rising exponentially to 10 per cent above 80 years). Then using Bayes' theorem, the post-test positive predictive value of testing this population is only 18/214 (eight per cent). This means that only eight per cent of persons who have a positive test result actually have the disease, the corollary being that 92 per cent of persons with a positive test result do not have the disease. This is not a suitable use of an investigation, no matter how high its sensitivity and specificity.

These two examples highlight why we must include a comprehensive history and examination to increase the pre-test probability of disease, before performing any investigations to confirm our clinical diagnosis; not the other way around.

Glaucoma continues to be the second commonest cause of blindness but the only preventable form of blindness. Fifty per cent of glaucoma remains undiagnosed, despite a significant proportion of patients visiting an eye-care provider within the previous year. Throwing investigations at the problem is not the answer. Instead, a comprehensive history and examination are essential. As a group, we can find the other 50 per cent.

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Management of

Brittany Becker BS
Leonid Skorin Jr
OD DO MS FAAO FAOCO

This aggressive form of glaucoma can be managed successfully by optometrists. Know your treatment options and when to enlist ophthalmologic help.

Neovascular glaucoma (NVG) is a sight-threatening condition that develops as a result of iris neovascularisation (NVI), otherwise known as rubeosis. The causative factor behind NVG is severe, diffuse, chronic retinal ischaemia that results in the production of vascular endothelial growth factor (VEGF). This is the body's attempt to revascularise the hypoxic retinal areas.[1,2] When VEGF diffuses into the anterior segment of the eye, it can initiate neovascularisation of the iris and of the anterior chamber angle (NVA). Both of these can impair aqueous outflow.[3,4] In severe cases, peripheral anterior synechiae formation can induce secondary angle-closure glaucoma.[1,2,5]

Numerous retinal ischemia causes can lead to rubeosis and subsequent NVG. Ischaemic central retinal vein occlusion (CRVO) accounts for about 33 per cent of NVG cases, with about 50 per cent of CRVO eyes developing NVG.[1] Fluorescein angiography (FA) can be used in CRVO cases to show the extent of the ischaemic retinal capillary non-perfusion to assess NVG risk. Another retinal ischaemia cause includes diabetes mellitus (DM), especially in those who have had the disease for more than 10 years.[3] Thirty-three per cent of patients with proliferative diabetic retinopathy (PDR) will develop rubeosis. The risk of NVG can be decreased with pan-retinal photocoagulation (PRP) treatment.[2] Other, less common causes of NVG include central retinal artery occlusion (CRAO), ocular ischemic syndrome (OIS), intraocular tumour, long-standing retinal detachment, trauma, sickle-cell retinopathy and chronic intraocular inflammation.[1,2,5]

Signs and symptoms

The patient may subjectively complain of a red eye, pain, decreased vision and photophobia. Conversely, they may be asymptomatic. If the intraocular pressure (IOP) elevation is acute or very high, the patient may experience nausea, vomiting and headache.[2] Objective ocular signs include conjunctival injection, corneal oedema, iritis, IOP elevation and ectropion uvea. Hyphaema may also occur.[2,4]

A hyphaema is graded based on the amount of anterior chamber filling. Microhyphaema has a single layer of red blood cells. Grade 1+ hyphaema will fill less than one-third of the anterior chamber (Figures 1 and 2). Grade 2+ hyphaema fills between one-third and one-half and a grade 3+ hyphaema fills over one-half of the anterior chamber. An anterior chamber that is completely filled with blood is known as an 'eight ball' hyphaema, or a grade 4+.[2]

Treatment of a hyphaema involves discontinuation of anticoagulant medication such as non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin, and remaining in an upright position of at least 30 degrees at all times, even during sleep.[2] A beta-blocker or carbonic anhydrase inhibitor are the best pharmacologic ways to control IOP that is elevated over 24 mmHg. Grade 2+ hyphaema or less is associated with a four per cent incidence of raised IOP.[1] Topical steroids such as prednisolone acetate 1% should be used four times per day to reduce inflammation. Mydriatics are controversial but scopolamine 0.25 per cent twice per day or atropine 1% once per day may be used. The more severe the hyphaema, the more aggressive the treatment should be.[1,2,5]

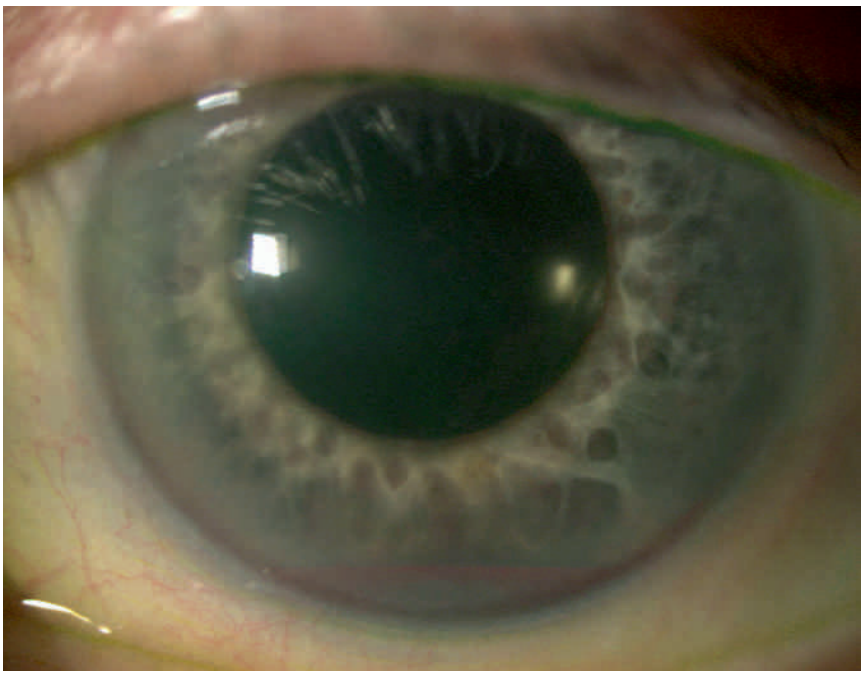

Figure 1. Grade 1+ hyphaema secondary to neovascular glaucoma caused by a previous central retinal vein occlusion

neovascular glaucoma

Grading neovascular glaucoma

NVG can be separated into three stages. The first stage of rubeosis iridis is characterised by tiny dilated capillary tufts found at the pupillary margin. These grow radially over the surface of the iris until it reaches the anterior chamber angle; however, NVA can be present without pupillary involvement, especially after CRVO. Treatment for rubeosis iridis involves PRP and VEGF inhibitors such as bevacizumab (Avastin) and ranibizumab (Lucentis).[1]

Secondary open-angle glaucoma is the second stage of NVG. This occurs when neovascular tissue proliferates across the face of the angle. The new blood vessels can connect to form a fibrovascular membrane that blocks the trabecular meshwork and aqueous outflow. This should be treated medically in the same way as primary open-angle glaucoma except that prostaglandin analogues should be avoided due to their inflammation promotion and poor uveoscleral access. VEGF inhibitors may be useful. PRP can still be performed but it will not reverse the fibrous component.[1]

The third stage is secondary angle-closure glaucoma. The fibrovascular tissue contracts and pulls the peripheral iris over the trabecular meshwork, forming a peripheral anterior synechiae (PAS). Treatment still involves medication, VEGF inhibitors, and PRP; however, it is better to administer VEGF inhibitors before PAS forms and the angle is closed.[4] Filtration surgery can be considered such as trabeculectomy or glaucoma drainage implantation.[1]

Trabeculectomy success is limited due to the severe inflammation found in NVG eyes. Success rates can be improved to 57.5 per cent over five years if trabeculectomy is used with mitomycin C (MMCT).[4] Valve implantation surgery is not always successful and may be due to the high amount of VEGF found in the aqueous humor;[6] therefore, VEGF inhibitors may prove useful for NVG management. They can temporarily decrease IOP and inflammation and may lead to better surgical success rates.[7] Used before MMCT, VEGF inhibitors were clinically shown to decrease the risk of post-surgical hyphaema.[8] Additionally, PRP can aid surgical success when used in conjunction with VEGF inhibitors and MMCT.[9] If the retina cannot be viewed for PRP treatment, then one should consider a pars plana vitrectomy with endolaser combined with glaucoma drainage implant.[4]

NVG prognosis is guarded and depends on detection and early treatment. PRP is the treatment of choice if the retina can be visualised.[2] Prognosis is poor because this disease is chronic and progressive.[4] Retrobulbar alcohol injections or chlorpromazine or enucleation may be necessary if the eye becomes unmanageably painful.[1,10]

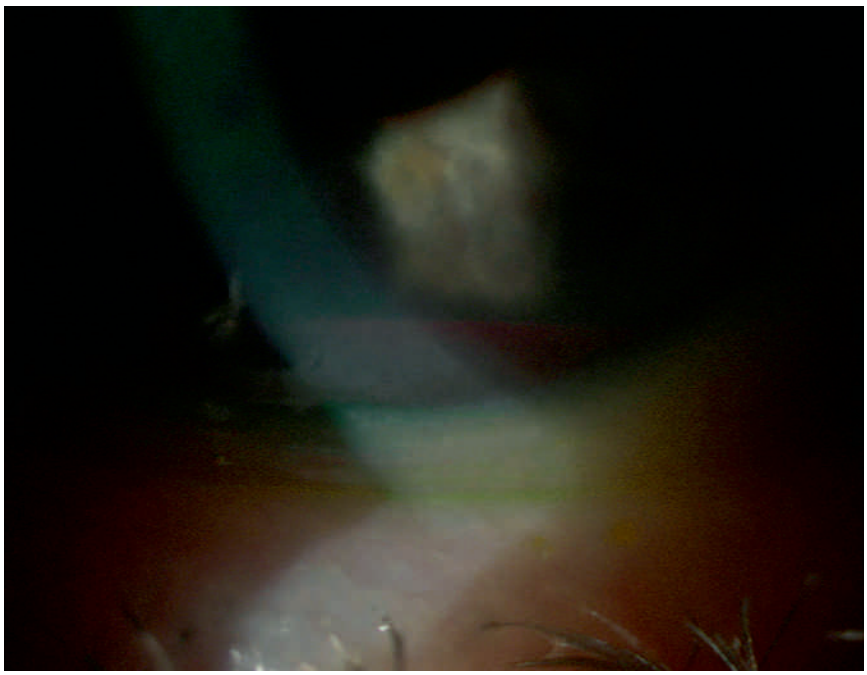

Figure 2. Magnified view of hyphaema showing layering of blood

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Technology aids clinical

Every glaucoma case is different

Understanding how instruments collect and analyse data is critical for interpretation and the best outcome for the patient

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Case report

A 59-year-old male presented for a glaucoma assessment. Unaided visual acuities were 6/4.8- right and 6/6 left. A glaucoma specific historical risk profile included his race (Hispanic) and a recent course of oral prednisone to treat a reaction to bed bugs. Intraocular pressures with applanation tonometry at 1:00 pm were 16 mmHg in the right and 17 mmHg in the left. Pachymetry values obtained with the Pentacam HR were thinner than average at 508 µm in the right eye and 511 µm in the left.

A slitlamp examination showed pseudoexfoliation in both eyes (Figure 1). Gonioscopy showed angles open to the ciliary body with moderately heavy pigmentation.

Optic nerves were small and oval with an apparently healthy neuro-retinal rim (NRR) and no apparent notching or thinning (Figures 2A and 2B). There was some minor temporal Beta peripapillary atrophy (PPA) with no evidence of Drance haemorrhages or retinal nerve fibre layer (RNFL) defects in either eye.

Cirrus optical coherence tomography (OCT) imaging (Figure 3) of the RNFL shows some minor asymmetries in the TSNIT curves with all parameters considered to be essentially within the normal range as compared to the instrument's normative database. The instrument has incorrectly identified the disc margins; the NRR thickness graph and cup-disc parameters should not be considered to be accurate representations of the anatomy.

Results obtained with the Heidelberg Retinal Tomograph (HRT3) Moorfields Regression Analysis confirm that the optic disc sizes are small (Figure 4). The analysis considers the NRR to be within the normal range in all sectors. Given the nature of this analysis relying on comparisons to a normative database, results need to be interpreted with caution as smaller disc sizes are less well represented in the instrument's database; however, the results do provide the start of a baseline for future comparison.

Visual field results with the Matrix FDT show good reliability indices for both eyes (Figures 5A and 5B). There are scattered isolated depressions in the right field result with the GHT considered within the normal limits in both eyes.

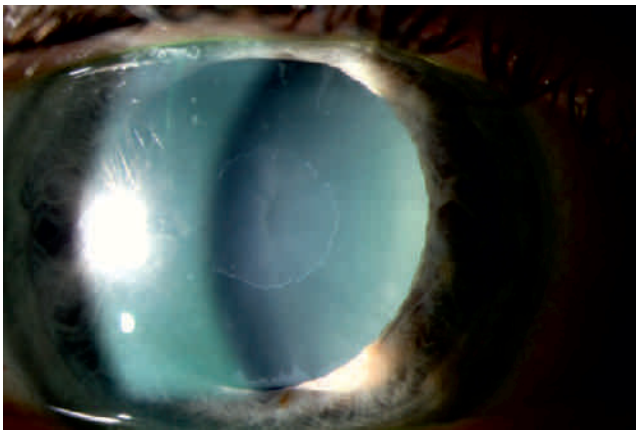

Figure 1. Slitlamp image of the anterior surface of the crystalline lens of the right eye

Summary

Pseudoexfoliation material is associated with abnormalities of the basement membrane in epithelial cells.

It can have a wide distribution throughout the body including vasculature, lung, skin, liver, heart, kidney, gallbladder, extraocular muscles and meninges. With respect to the eye, the iris pigment epithelium, ciliary epithelium and the peripheral anterior lens epithelium can all produce pseudoexfoliative amyloid-like material.[1]

work-up

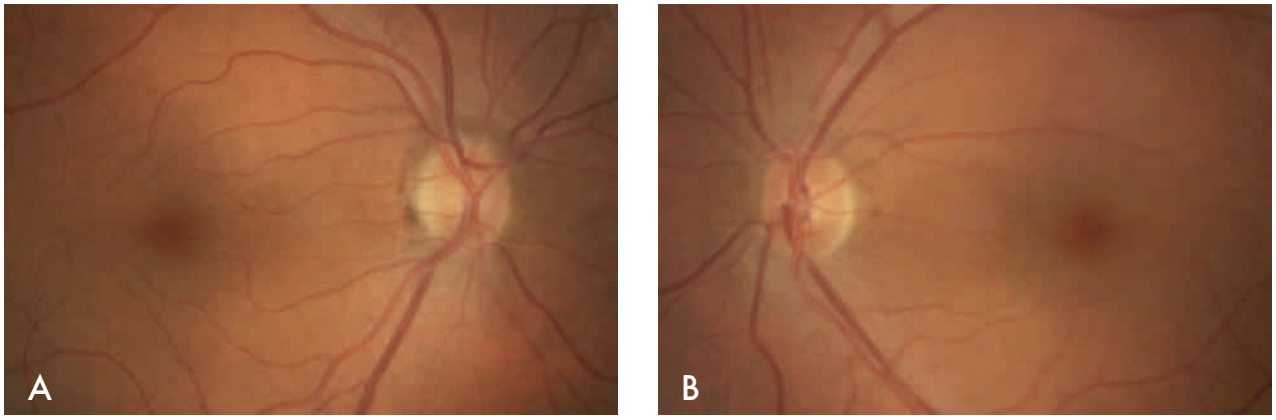

Figure 2. Fundus images of the right (A) and left (B) posterior poles

This patient has a low to moderate historical risk profile for glaucoma. He has IOPs within the normal range but thinner than average pachymetry values. He has pseudoexfoliation syndrome but there is no conclusive evidence of progression to pseudoexfoliative glaucoma at this point in any of the imaging findings, funduscopic appearance of the disc or visual field results.

There is often no definitive answer for the management of glaucoma suspects, as it is based on a case by case basis. An appropriate management plan in this case would include phasing of the IOPs and following this, repeated visual fields and stereoscopic disc assessment in six months. Repeated imaging annually is also indicated. As three examinations are required to produce change analysis from the imaging instruments, repeating the tests at the six-month visit may also be considered to allow subsequent change analysis to be produced at the end of the initial 12-month period.

Imaging modalities are playing an increasing role in eye disease and in particular in the detection and monitoring of glaucoma suspects and glaucoma patients. A detailed understanding of the underlying anatomy and physiology, as well as experience with and understanding of the instruments' method of collection and analysis of data, are critical to result interpretation and maximising their benefits.

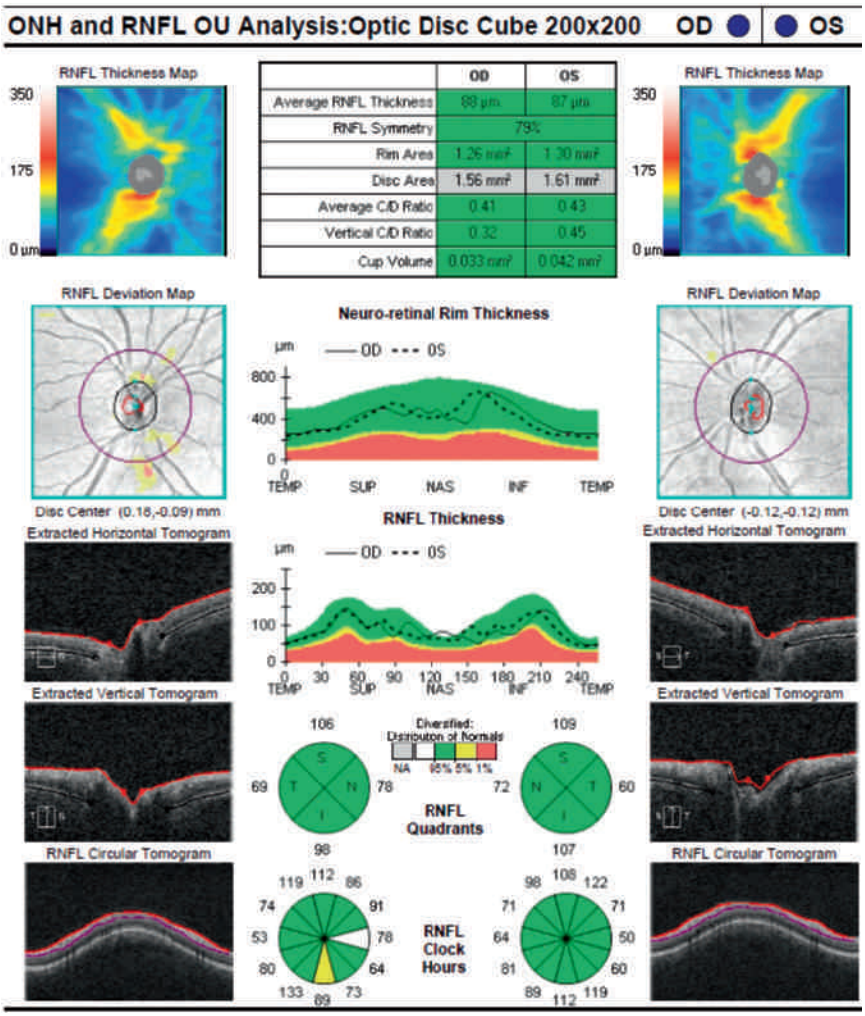

Figure 3. Cirrus OCT results

1. Pseudoexfoliation Glaucoma. Pons ME. Medscape article http://emedicine.medscape.com/article/1206366-overview#a0101.

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Technology aids clinical work-up

From page 25

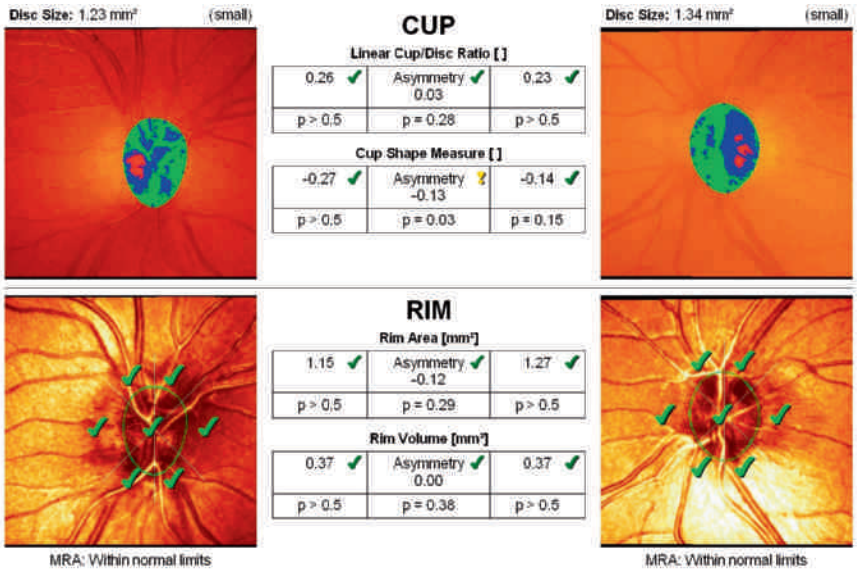

Figure 4. HRT3 results suggesting that the NRR is within the normal range

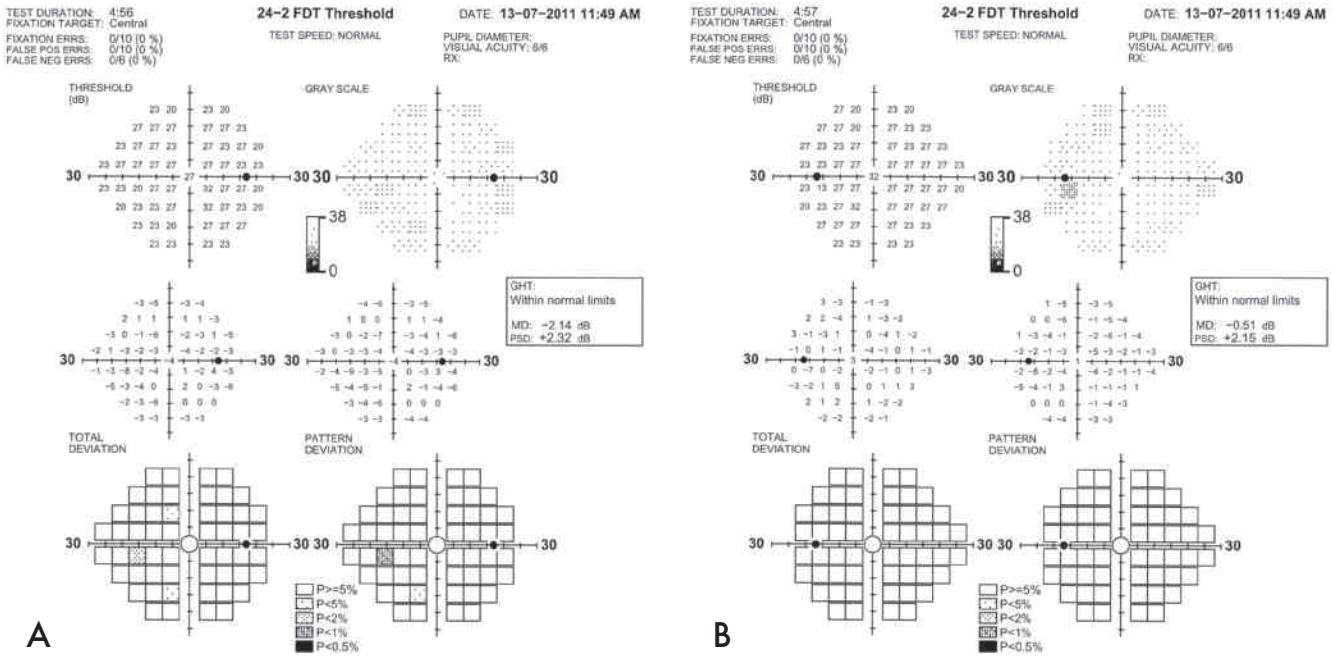

Figure 5. Matrix visual field results for the right (A) and left (B) eye

Briefs

Check for link between vision and hearing loss in elderly

A link between poor vision and hearing loss in the elderly has prompted researchers to recommend optometrists enquire about a patient's hearing.

American researchers discovered that three measures of low-contrast visual acuity were associated with moderate bilateral hearing loss among 446 adults with a mean age of 79.9 years.

The three measures associated with hearing loss were overall low contrast acuity, low contrast acuity at low luminance, and low contrast and acuity in glare.

The study found normal and high-contrast acuity measures were not significantly associated with hearing loss.

The researchers cited evidence that dual sensory loss can increase effects of depression, quality of life and cognitive function compared with the loss of either hearing or vision alone.

Schneck ME, Lott LA, Haegerstrom-Portnoy G, Brabyn JA. Association between hearing and vision impairments in older adults. *Ophthalmic Physiol Opt* 2012; 32: 1: 45-52.

Drug preservatives inflame debate

American academics are embroiled in a debate about the rise of preservative-free glaucoma medication. A research group named the Valeant Working Group on Preservative Toxicity has claimed preservatives in medication can kill cells and cause inflammation unrelated to glaucoma, leading to increased risk during surgery.

The academics in the working group are funded by Valeant Pharmaceuticals.

American Academy of Ophthalmology clinical correspondent Dr Richard Bensinger said that preservatives in glaucoma medication issues were minimal, though he said toxicity issues from the preservative thiomersal were real and many medications were phasing out the compound.

Harrison L. Glaucoma drug preservatives: disease or minimal problem? Epub http://www.medscape.com/ophthalmology, 20 April 2012.

Baerveldt implants can perform better than Ahmed

Yale University researchers have found the Baerveldt ocular implant more effective than the Ahmed ocular implant for patients with severe glaucoma.

The trial followed 238 patients over three years. Seventy per cent of participants were pseudophakic, 50 per cent had primary open-angle glaucoma, 21 per cent had neovascular glaucoma and 10 per cent had uveitic glaucoma.

Researchers defined success for the implants as achieving an intraocular pressure between 5 and 18 mmHg. Participants were measured to see if there was a 20 per cent reduction in pressure following surgery, and monitored for side-effects three months following surgery.

Baerveldt implants achieved 11 per cent success while Ahmed implants achieved only four per cent success. Researchers noted the Baerveldt's filtration area was double that of the Ahmed.

The participants will be followed for a further two years before the final results are reported.

American Glaucoma Society 22nd Annual Meeting: Abstract 1. Presented March 1, 2012.

What is role of neurology in glaucoma?

A paper in *Ophthalmology* has argued for greater discussion and examination of glaucoma from the perspective of a symptom of neurological decline.

Dr Elma Chang and Dr Jeffrey Goldberg studied the decay of retinal ganglion cells not from the point of view of increased ocular pressure but instead from the susceptibility from pressure caused by existing neurological links with the brain.

The paper outlines several models of neuro-degeneration informed by evidence of the worsening of retinal ganglion cells seen in the optic nerve head.

Chang E, Goldberg J. Glaucoma 2.0: Neuroprotection, Neuroregeneration, Neuroenhancement. *Ophthalmology* 2012; cited 2012 20 April. Available from: http://www.sciencedirect.com/science/article/pii/S0161642011010499.

Caffeine may help glaucoma sufferers' dry eye but at what cost?

Coffee could increase glaucoma risk and provide relief for dry eye patients, according to two separate studies.

Researchers at Harvard Medical School in the United States found a positive association between heavy coffee drinking and the development of exfoliation glaucoma in more than 75,000 women.

Lead investigator Dr Louis Pasquale said that previous randomised trials indicated that homocysteine levels, a risk factor for coronary disease, were increased after caffeine consumption; patients with exfoliation glaucoma had increased levels of homocysteine in the aqueous humour and tear.

Another study, conducted at the University of Tokyo's School of Medicine, showed that caffeine intake can increase the eye's ability to produce tears, which could help improve treatment of dry eye syndrome.

Based on earlier research that had shown a reduced risk of dry eye in caffeine users, the study assessed the amount of tear secretion in 78 participants both after consuming caffeine and then a placebo.

Tear volume was measured 45 minutes after consumption and during a time when tear production was usually stable.

FDA approves Zioptan

The American Food and Drug Administration has approved Zioptan, a preservative-free prostaglandin solution used to treat elevated intraocular pressure in patients with ocular hypertension and open angle glaucoma. The drug, produced by Merck, was trialled in five clinical studies involving over 900 patients. Trials found Zioptan lowered IOP at three months by 6-8 mmHg and at six months by 5-8 mmHg. Similar to all prostaglandins, the solution has side-effects leading to increased thickness and length of eyelashes.

Aflibercept in the age-related

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and
Biogram Inc, FL USA

Fusion protein based molecules are becoming more important in treating eye disease, including macular degeneration, but researchers must look to gene therapy for cures.

Aflibercept is a fusion protein that has been used with some success as a cancer treatment. This biological molecule was also approved in 2011 for use in the treatment of age-related macular degeneration due to its anti-neovascularisation properties. This article discusses the role of aflibercept in ophthalmology and provides information on the chemical make-up of the fusion protein molecule and how it functions.

Introduction

Over the past several decades there has been an emphasis on the development of new categories of ophthalmic drugs and biologics. Some of these drug and biologics stand alone and others are used more effectively in combination with other products. Many of these compounds are used for what at first glace may be entirely different indications.

Aflibercept is a fusion protein that has been used as an anti-cancer treatment for a variety of different indications, including urothelial cancer, pancreatic cancer, prostate cancer and non-small cell lung cancer.[1,2,3] The reported results were mixed with some evidence of side-effects or only modest efficacy. Aflibercept is also being used as an ophthalmic treatment.

Regardless of the indication, the target molecule for aflibercept (known as VEGF-F Trap) is vascular endothelial growth factor (VEGF).[4,5,6] VEGF—also known in older literature as vascular permeability factor, VPF—has a pivotal role in enhancing vascular permeability and is linked to the development of age-related macular degeneration (AMD) and macular oedema. The syndrome of hyperpermeability also caused by VEGF can lead to ascites leakage (systemically). This is defined as ascites contaminated with transformed cells. Hyperpermeability is indicative of late-stage disease, ineffective treatment or treatment failure. VEGF will continue to promote the formation of blood vessels into both normal and neo-plastic tissue if left unchecked.

Aflibercept was approved for use in Australia by the TGA on 7 March 2012. The drug product, called Eylea, can be injected into the eye less frequently than the current standard, Genentech's Lucentis (ranibizumab).

In the United States, Eylea is slightly less expensive, at $1,850 an injection versus $1,950 for Lucentis.

Eylea will be on the market in Australia within the next six months and a price has not yet been set. Currently, Lucentis costs $1,976 per injection in Australia and is PBS-subsidised.

Chemistry

Aflibercept is a fusion protein that functions as an inhibitor of all six forms of VEGF.[7,8] It has a molecular weight of 96.90 kDa and a formula of $C_{4318}H_{67898}N_{1164}O_{1304}S_{32}$. It is a molecule consisting of the intracellular domains of VEGF receptors 1 and 2. These receptors are fused to the Fc regions of human IgG, thus forming the (fusion) protein. The higher binding affinity (theoretical), should translate to a longer duration of action *in situ*.

The molecule is produced in Chinese hamster ovary (CHO) cells that extrude excessive amounts of the protein. The cell line has been modified by recombinant techniques. VEGF-Trap has a half-life of about 17 days systemically. The half-life in the ocular space is unknown at this time.

Pre-clinical

Cao and colleagues demonstrated that aflibercept prevented the development of choroidal neovascularisation (CNV) in Sprague-Dawley rats when administered by sub-retinal injection.[9] In a further series of experiments, Cao showed that when VEGF-Trap was administered 10 days following onset of CNV in this rat model, the fusion protein was able to modulate further progression of neovascularisation.

Lutty and colleagues performed a study in dogs that had undergone oxygen-induced retinopathy (OIR).[10] The study showed that a single intravitreal injection of VEGF-Trap will prevent intravitreal neovascularisation. The effects were observed over a dosage range of 250, 25 and 5 µg/eye. A regression of neovascular membranes was also reported.

Ophthalmic clinical use of aflibercept

The World Health Organization estimates that there are in excess of 150 million persons in the world who are visually impaired. Many of their diseases such as glaucoma and age-related macular degeneration (AMD) remain undiagnosed until the disease has progressed substantially to cause pain (in the case of glaucoma) or a noticeable loss of vision. In the case of AMD, neovascularisation of the retinal space is responsible for about 90 per cent of the cases involving severe vision loss. AMD can be sub-diagnosed on the basis of whether the disease is dry or wet.

treatment of macular degeneration

Dry AMD occurs when there is no neovascularisation into the retinal space; dry AMD can occur with mild amounts of drusen up to geographic atrophy. Micronutrient therapy that contains high amounts of carotenoids such as are found in green leafy vegetables has reduced the rate of disease progression, especially in non-smokers without weight control issues. These supplements are taken orally.

In addition to the surgical option, there have been various biologic and drug therapies that have been developed within the past decade. Most of these are VEGF antagonists or binding agents. VEGF-Trap reported as aflibercept is such a therapy.

Aflibercept has been used with good success in a phase 1 clinical trial for the treatment of CNV in AMD patients.[11] Nguyen and colleagues conducted a phase 1 double-masked placebo-controlled study in 18 patients with neovascular AMD.[11] This study was termed Clinical Evaluation of Anti-angiogenesis in the Retina (CLEAR). The study design involved intravenous (ascending) dosing of VEGF-Trap with placebo, 0.3, 1.0 and 3.0 mg/kg.

During the course of the study, a dose-dependent increase in systemic blood pressure was observed in the study group. The increase in blood pressure was noted about 1.0 mg/kg. As a result, further systemic studies were halted; however, according to the available data it seems that the drug did have some effect on controlling CNV.

Another phase 1 study, CLEAR IT-1, was an escalation study using an intravitreal injection as the inoculation route for the VEGF-Trap.[12] This range-finding study comprised a dosing regimen consisting of 00.05, 0.15, 0.5, 1.2 and 4 mg. The study was designed as single intravitreal injection of multiple doses. The results of the study showed a mean visual gain of 4.8 letters and mean OCT central retinal thickness decrease of 298 µm to 208 µm.

The DA VINCI Study was a phase 2 study conducted in patients with diabetic macular oedema using VEGF-Trap as the treating agent.[13] The study was designed as a double-masked randomised, multi-centre trial. The 221 patients who were enrolled in this range-finding study were assigned to one of five treatment groups:

- 0.5 mg VEGF-Trap every four weeks
- 2 mg VEGF-Trap every four weeks
- 2 mg VEGF-Trap, three initial doses followed by every eight weeks
- 2 mg VEGF-Trap, three initial doses and then on an as-needed basis
- macular laser photocoagulation (control).

The study concluded at 24 weeks with measurements in mean visual acuity and corneal thickness. All four VEGF-Trap treatment groups were found to yield statistically better outcomes than the macular laser group against which they were being measured. This was true for both measured parameters. Clearly, the route of inoculation is key to the success of the drug in disease treatment.

Conclusion

The scientific literature is evolving in relation to the overall field of fusion proteins and cancer treatment or other medical uses.[14] It may be more significant that these fusion proteins may be used for indications that at first, may seem to be vastly different.

Aflibercept and other fusion protein based molecules will become of increased importance, at least in the short term, in treating various disease states including macular degeneration and other diseases of the eye. As with all drugs and biologics for this condition, these are disease treatments, not cures. The actual cure probably lies in the realm of gene therapy, which is some years away from practical reality.

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Glaucoma costs to double

Selective laser trabeculoplasty (SLT) may be the solution to prevent an explosion in the total cost of primary open-angle glaucoma in Australia.

In a paper published in *Clinical and Experimental Ophthalmology*, researchers say the prevalence of glaucoma will increase from 208,000 in 2005 to 379,000 in 2025, due to Australia's baby-boomer age group.

Under the current health system, total costs would soar from $1.9 billion in 2005 to $4.3 billion in 2025.

Professor Jonathan Crowston is the managing director of the Centre for Eye Research Australia. He says economic modelling suggests that early interventions for SLT on glaucoma patients, assuming the treatment is at least as effective as eye-drop medication, could have a dramatic return on investment in comparison to ordinary treatments–up to $13.82 per dollar if it reduced progression by 50 per cent.

SLT has been used for only eight years and no evidence is available on whether early SLT can bring side-effects. Professor Crowston admits that he does not currently advise early SLT.

'We don't know if you have laser first, whether drops are going to be as effective as they could have been if you had prescribed drops first. That is important because if the treatment impairs the drops, it may bring forward the patient's time before surgery,' he said. 'It is a concern I have.'

Professor Crowston says SLT is a 'gentler' laser treatment but it works on only 70 to 80 per cent of patients.

As a result of the economic modelling, the National Medical Health and Medical Research Council is providing funding of $614,240 for a four-year study to investigate the potential of early SLT. Associate Professor Ecosse Lamoureux will be a chief investigator for the research.

Centres are being established in Adelaide, Melbourne, Sydney and Brisbane to examine if early SLT can assist Australia when the baby-boomers begin to be diagnosed with glaucoma.

Professor Crowston says Australia's low rate of glaucoma diagnosis is similar in the UK and America. Here, 59 per cent of glaucoma cases had previously been undiagnosed despite a visit to an eye-care provider in the previous year. Economic modelling has found that if higher diagnosis rates are achieved, health system costs will increase.

'What the model tells us is that if we were to do that, it would go some way to reduce avoidable blindness but it would be expensive; however, when you look at the overall cost of the burden of disease, it would be cost effective,' he said.

Dirani M, Crowston J et al. Economic impact of primary open-angle glaucoma in Australia. *Clinical and Experimental Ophthalmology* 2011; 39: 623-632.

Patient support services

Glaucoma Australia is the peak glaucoma awareness, education and support association in Australia. It assists eye health professionals by providing information and support to help patients and their families to work through issues brought about by the condition.

Services provided by Glaucoma Australia include:

- support for those with glaucoma, their family and carers
- patient education and awareness activities at the local and national level
- dissemination of information in several languages and via a subscription newsletter
- glaucoma support groups.

Optometrists are urged to tell their patients about Glaucoma Australia and how to contact it: telephone (02) 9906 6640, email glaucoma@glaucoma.org.au and visit www.glaucoma.org.au.

Age-related macular degeneration (AMD) is the leading cause of visual loss for adults in the developed world.[1-4] In 2004, it was estimated that more than 48,000 Australians had visual impairments from AMD. In two large Australian population-based studies, the Visual Impairment Project (VIP) and the Blue Mountains Eye Study (BMES), the prevalence of early AMD was between 5.8 per cent and 15.1 per cent, with prevalence increasing with age.[1,3,4]

Around 15 per cent of people over 50 years of age, about 750,000 Australians, have some signs of AMD. The prevalence of early changes rises exponentially with age, so that nearly two out of three people who reach the age of 90 years will have early AMD, with one in four having a significant loss of vision as a result of progressive to late AMD. With a rapidly ageing population, the burden of visual impairment secondary to AMD is projected to double by 2020, with substantial social and financial costs. AMD cost Australia $2.6 billion in 2005 and according to a report prepared by Access Economics for the Centre for Eye Research Australia, this figure is expected to grow to $6.5 billion over the next 20 years.

AMD is broadly classified as either dry (atrophic, non-exudative) or wet (neovascular, exudative). Individuals with wet AMD suffer a precipitous and profound loss of vision secondary to the development of a choroidal neovascular membrane (CNV). Until recently, the mainstay of treatment for wet AMD was laser argon photocoagulation and photodynamic therapy (PDT).[5-8] Argon laser is effective for extrafoveal lesions but has limited success for lesions closer to the centre of the fovea. PDT is not effective in restoring vision in wet AMD and is not cost-effective.

The recent widespread use of antibodies directed against the vascular endothelial growth factor (anti-VEGF antibody) has revolutionised the treatment of AMD and is having a major impact on reducing rates of blindness. Vascular endothelial growth factor (VEGF) is the central molecular mediator of wet AMD.[9] The evidence implicating VEGF in the development of neovascular AMD is strong. VEGF appears to play an orchestrating role in the extremely complex molecular events of angiogenesis and neovascularisation (new blood vessel formation).[10-13] Considerable evidence indicates that VEGF, specifically the VEGF-A isoform, stimulates CNV and vascular permeability and subsequent leak.

The role of VEGF-A is supported by a strong positive correlation between

Needleless injection

Novel system for non-invasive delivery of drugs to the interior eye

Dr Hong Zhang
MBBS MD MS PhD
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Centre for Eye Research Australia
University of Melbourne

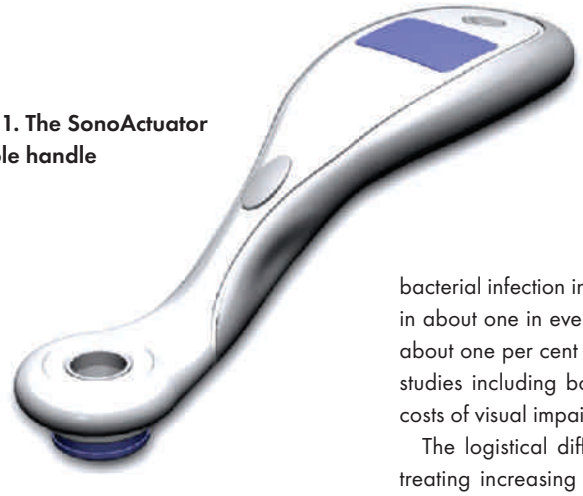

Figure 1. The SonoActuator reusable handle

intraocular VEGF-A levels and blood vessel formation in patients with diabetic retinopathy and other VEGF-A dependent retinal disorders.[14-16] In non-human primates, intraocular injection of VEGF-A has resulted in dose-dependent iris neovascularisation, whereas VEGF-A neutralisation prevented this. In a primate model of laser-induced CNVM, intravitreal anti-VEGF-A administration decreased both retinal neovascularisation and vascular permeability. Immunohistochemical studies have shown that surgically-excised membranes stain strongly for VEGF and post-mortem studies of eyes with wet AMD demonstrate significantly higher levels of VEGF in the RPE and outer nuclear layer than those in AMD-free controls.[17-20]

While the treatment is effective in slowing or stopping the progression of AMD, anti-VEGF treatment needs to be administered on a regular basis once initiated, usually monthly; vision loss occurs if treatment is discontinued. In humans, the advent of intravitreal injection of anti-VEGF antibodies, for example, bevacizumab (Avastin) or functional fragments of antibodies, for example, ranibizumab (Lucentis) has dramatically transformed the treatment of wet AMD, with remarkable improvement in vision in a very high proportion of patients.[13,21,22]

This requires frequent intravitreal injections for life—as often as four-weekly—with the concomitant risks associated with that invasive intraocular procedure. These risks include infection, retinal detachment, cataract and inflammation with potential for permanent visual loss. Patients also occasionally suffer pain and frequently experience discomfort for one to three days after the intraocular injection. The most feared complication of intra-vitreal injections, bacterial infection inside the eye, occurred in about one in every 2,000 injections, or about one per cent of the patients in these studies including both direct and indirect costs of visual impairment.

The logistical difficulty associated with treating increasing numbers of AMD sufferers with the regimens required (monthly injections) have begun to emerge. This has led to the identification and investigation of other potential methods of drug delivery in a cost-effective manner. The current gold standard for delivery of drugs to the back of the eye is needle injection, so the appeal of a non-invasive device with proven safety and efficacy is compelling.

Figure 2. The SonoPod disposable sterile gel pack contains the drug to be delivered

Ultra-sound delivery

The SonoEye device, which was invented by Seagull Technology, is an ultra-sound delivery device that permits non-invasive delivery of anti-VEGF antibodies into the eye. It has been demonstrated to deliver molecules such as bevacizumab non-invasively into rabbit eyes, specifically to the retina.

The device consists of two components. The SonoActuator (Figure 1) is a reusable handle that contains the system electronics and drug delivery indicator. The other component is the SonoPod (Figure 2), a disposable sterile gel pack that contains the drug to be delivered.

The device uses the electrical properties of polymers combined with ultrasonic stimulation to facilitate the release of drugs (with or without nano-particle encapsulation) in regulated doses and subsequent movement of packaged or raw drugs across biological membranes (Figure 3). It works by incorporating a measured dose of anti-VEGF antibody into a gel to facilitate the

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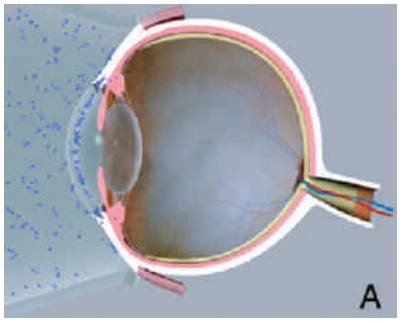
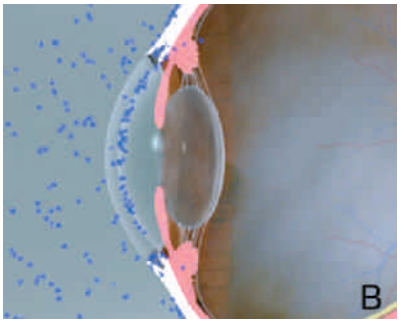
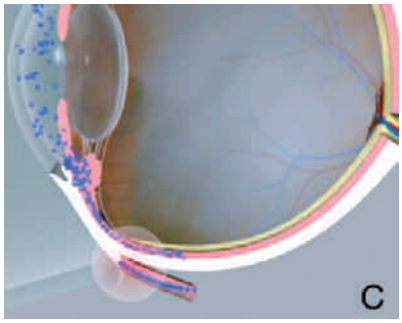


Depending on its intended use, the SonoPod may contain single or multiple drug doses



Drugs enter the eye via the cornea, conjunctiva and sclera



The SonoPod contour can selectively target the anterior and posterior segment of the eye

Figure 3. How the SonoPod works

Needleless injection

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regulated release and subsequent movement of the antibody across the surface of the eye and into the retina. Studies have shown that drugs ranging in size from larger proteins to small molecules can be successfully delivered to the eye.

Ultrasonic energy is already used in eye surgery and cataract surgery and is safe on the outside of the eye. The device uses an innovative combination of nanotechnology and ultrasound to deliver medication that can specifically target the retina. The benefits of the device would be that it is painless, easy to use and potentially could be administered by the patients themselves.

Researchers of the Centre for Eye Research Australia are conducting research using the SonoEye device. The device has the ability to become a non-invasive alternative to injections into the eye and could eventually eradicate the need for some surgical interventions. While the study that is to be undertaken with CERA relates to macular degeneration, the device also has a place in the treatment of diabetic retinopathy, inflammatory eye disease and other conditions of the back as well as the front segment of the eye.

Continued development is supported by a National Health and Medical Research Council Development Grant. Scientists are conducting trials to assess the safety and efficacy of the device, and aim to conduct a safety study in a small number of AMD patients this year.

Significance

The ability to non-invasively deliver anti-VEGF IgG into the eye could have a major impact on cost-saving and alleviating workload for ophthalmologists. Recent clinical studies have also demonstrated the efficacy of anti-VEGFs in a wide number of other blinding retinal diseases, further supporting the need for a non-invasive delivery system. The ability to deliver large complex proteins and biologicals non-invasively into the eye also holds great promise for transforming the treatment of other retinal and optic nerve disease.

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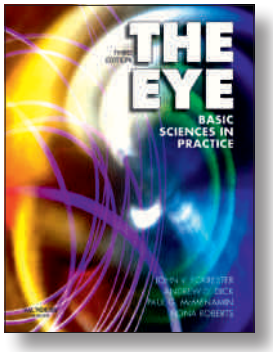

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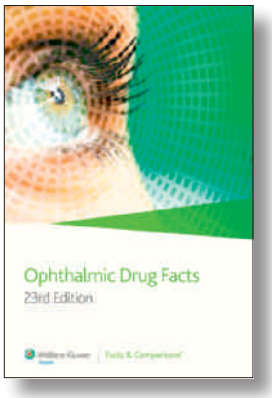

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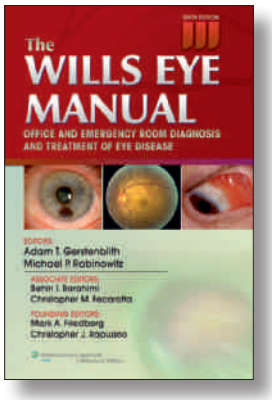

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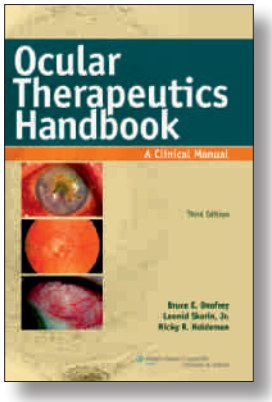

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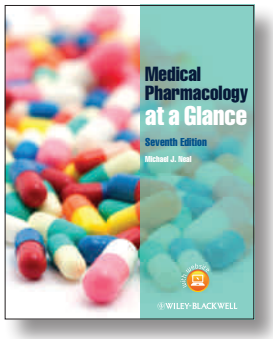

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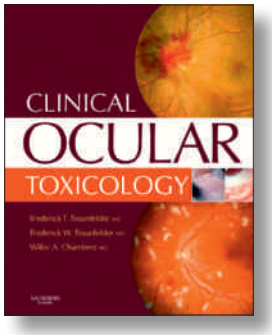

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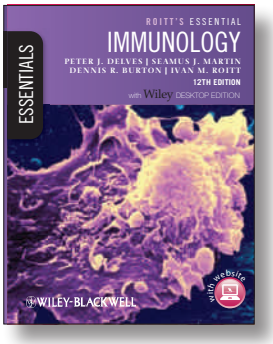

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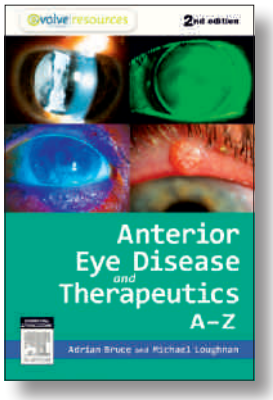

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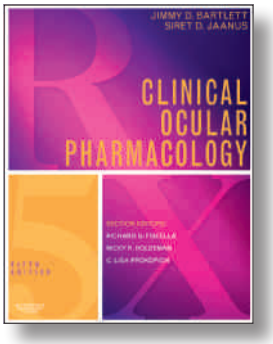

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