May 2005  (Volume 89, Number 5).

**Special Data Supplement for this Issue**

**BJO at a glance**

BJO at a glance
Creig Hoyt

**Editorials**

Hydroxychloroquine screening
A G Lee

Vision restoration therapy
B A Sabel, S Kenkel, and E Kasten

**Commentaries**

Minding the gap
D A Harrison

How to assess the prevalence of trachoma
H R Wright, H Vu, and H R Taylor

**Echo**

Long sight reduces learning in young schoolchildren
Clinical science - Scientific reports

Limbal epithelial crypts: a novel anatomical structure and a putative limbal stem cell niche
H S Dua, V A Shanmuganathan, A O Powell-Richards, P J Tighe, and A Joseph

Anti-TNF-α therapy for sight threatening uveitis
E W Lindstedt, G S Baarsma, R W A M Kuijpers, and P M van Hagen

Clinical evaluation of the pressure phosphene tonometer in patients with glaucoma
E Rietveld, D A van den Bremer, and H J Völker-Dieben

Intraocular pressure variability in patients who reached target intraocular pressure
F K Malerbi, M Hatanaka, R M Vessani, and R Susanna, Jr

A novel index for predicting intraocular pressure reduction following cataract surgery
S A Issa, J Pacheco, U Mahmood, J Nolan, and S Beatty

Effects of the combination of bimatoprost and latanoprost on intraocular pressure in primary open angle glaucoma: a randomised clinical trial
L M Doi, L A S Melo, Jr, and J A Prata, Jr

28 000 Cases of age related macular degeneration causing visual loss in people aged 75 years and above in the United Kingdom may be attributable to smoking
J R Evans, A E Fletcher, and R P L Wormald

An interinstitutional comparative study and validation of computer aided drusen quantification
V Sivagnanavel, R T Smith, G B Lau, J Chan, C Donaldson, and N V Chong

Radial optic neurotomy for ischaemic central vein occlusion
Optical coherence tomography characterisation of idiopathic central serous chorioretinopathy
J A Montero and J M Ruiz-Moreno

Evaluation of internet websites about retinopathy of prematurity patient education
E N Martins and L S Morse

Clinical science - Extended reports

Threshold Amsler grid as a screening tool for asymptomatic patients on hydroxychloroquine therapy
A Almony, S Garg, R K Peters, R Mamet, J Tsong, B Shibuya, R Kitridou, and A A Sadun

Long term outcome of trichiasis surgery in the Gambia

Corneal sensation after myopic and hyperopic LASIK: clinical and confocal microscopic study
M A Bragheeth and H S Dua

Efficiency of blood culture bottles for the fungal sterility testing of corneal organ culture media
G Thuret, A Carricajo, A C Vautrin, H Raberin, S Acquart, O Garraud, P Gain, and G Aubert

Infective keratitis in older patients: a 4 year review, 1998–2002
T K H Butler, N A Spencer, C C K Chan, J Singh Gilhotra, and K McClellan

Filtering bleb function after clear cornea phacoemulsification: a prospective study
J Klink, B Schmitz, W E Lieb, T Klink, H-J Grein, J Sold-Darseff, A Heinold, and F Grehn

The origins of polypoidal choroidal vasculopathy
M Yuzawa, R Mori, and A Kawamura

ANCA associated pauci-immune retinal vasculitis
M J Gallagher, K G-J Ooi, M Thomas, and M Gavin
Causes of severe visual impairment and blindness in schools for visually handicapped children in Iran
S A Mirdehghan, M H Dehghan, M Mohammadpour, K Heidari, and M Khosravi

How patients experience progressive loss of visual function: a model of adjustment using qualitative methods
R Z Hayeems, G Geller, D Finkelstein, and R R Faden

The development of the Indian vision function questionnaire: field testing and psychometric evaluation
S K Gupta, K Viswanath, R D Thulasiraj, G V S Murthy, D L Lamping, S C Smith, M Donoghue, and A E Fletcher

Penetration of moxifloxacin into the human aqueous humour after oral administration
G Kampougeris, A Antoniadou, E Kavouklis, Z Chryssouli, and H Giamarellou

Laboratory science - Extended reports

Corneal graft rejection occurs despite Fas ligand expression and apoptosis of infiltrating cells
K A Williams, S D Standfield, J R Smith, and D J Coster

Letters

Disappearance of eyelid xanthelasma following oral simvastatin (Zocor)
C L Shields, A Mashayekhi, J A Shields, and P Racciato

New onset diplopia: 14 years after retinal detachment surgery with a hydrogel scleral buckle
I Leibovitch, J Crompton, and D Selva

Inverse globe retraction syndrome complicating recurrent pterygium
A O Khan

Seeing is not believing
S J Hickman, D Alvares, H Crewes, R J Wise, and A N Gale
Radial optic neurotomy in combined cilioretinal artery and central retinal vein occlusion
S Mennel, K Droutsas, C H Meyer, J C Schmidt, and P Kroll

Mailbox

Value based medicine
S M Kymes, K D Frick, M Brown, and G C Brown

Cystoid macular oedema with trypan blue use
H K L Yuen, R F Lam, D S C Lam, P Gouws, and P Simcock

Book reviews

The History of Moorfields Eye Hospital, Volume III
R Grey

Corrections

CORRECTION

CORRECTION

From the library

From the Library
Hydroxychloroquine screening
A G Lee

Who needs it, when, how, and why?

Amonyp et alreport in this issue of theBJO(p 569) the use of athreshold Amsler grid (TAG) as a screening tool for asymptomatic patients taking hydroxychloroquine (HCQ). They studied 56 patients taking HCQ and 12 controls. Patients were tested with a “white on black” Amsler grid (AG), a “red on black” AG (RAG), and the threshold AG (TAG). TAG uses cross polarising filters to reduce the perceived luminance of the grid. Scotomas were detected in two patients (3.6%) with the standard AG and five patients (8.9%) with RAG, but 25 (45%) patients with TAG. The TAG testing detected the two positive AG screens and the five positive RAG screens. The authors concluded that TAG has increased sensitivity to the detection of subtle scotomas in patients taking HCQ. Unfortunately, because there is no “gold standard” for HCQ retinopathy in asymptomatic or presymptomatic patients without visible retinopathy the specificity of the TAG results is unknown.

If the scotomas seen on TAG were also detected reproducibly in the same location using another central field test (for example, Humphrey 10-2) this would provide evidence for the specificity of the TAG findings. I would encourage the authors to continue to follow their cohort of HCQ treated patients and perhaps even test the patients with the abnormal TAG findings again with an automated (Humphrey) 10-2 strategy or even a multifocal electroretinogram (MERG). Although the sensitivity and specificity of MERG in HCQ toxicity continues to be explored it may be that objective electrophysiological testing might be superior to subjective tests of visual function like the AG.1

One of the patients in this study (case 63) was only taking HCQ for 1 month and yet had large bilateral central scotomas. It is unlikely that this represented HCQ retinopathy and this patient did not have a baseline eye examination. This case demonstrates the limitations of not specifically excluding from the study any patients who did not have complete ophthalmological examinations before starting HCQ. It may be that false positive screens may be a significant limiting factor for the TAG. Pluennike and Blomquist reported that 6–11% of HCQ and control patients tested with RAG had a false positive result.2 The false positive rate for the TAG is not known from the study by Almony et al.

Although there have been many guidelines in the United States, Canada, and the United Kingdom for screening examinations for patients taking HCQ, the cost effectiveness and diagnostic yield of these recommendations have not been evaluated in a rigorous and critical evidence based manner.3 The risk of HCQ toxicity is exceedingly rare for low risk patients and over one million patients up to 2002 have been treated with HCQ with only 20 cases of toxicity at the “subthreshold” dose of <6.5 mg/kg/day. All of these 20 cases had taken the drug for more than 5 years. In addition, there still remains controversy as to the timing and content of screening examinations for these patients. The American Academy of Ophthalmology (AAO) has provided a screening strategy composed of three parts: (1) informed consent obtained by the prescribing primary physician with explicit written documentation in the medical record; (2) detection and minimisation of toxicity rather than prevention itself; (3) definition of high and low risk patients (see table 1); and (4) stratification of screening based upon risk factors. If a baseline eye examination is normal and the patient is taking a low dose (<6.5 mg/kg/day) of HCQ then the recommended screening interval follows the AAO screening recommendations for regular eye examinations in the general population. Annual screening was recommended for patients with higher or unknown dose or duration (>5 years) of HCQ therapy.3 Almony et al recorded several of the risk factors proposed by the AAO (see table 1) for HCQ retinopathy including weight adjusted doses, duration of HCQ therapy, and the age of the patients. They did not however include data on renal or hepatic insufficiency and no patients had documented other macular pathology.

The specific recommendation of the American Academy of Ophthalmology is for a baseline examination (listed in table 2) for all patients starting HCQ treatment. Unfortunately, there is no “gold standard” for identification of toxicity before the development of the ophthalmoscopic changes (that is, pigmentary changes and “bull’s eye maculopathy”). Despite the recommendation of the AAO, it is not clear that a baseline examination is cost effective given the large numbers of patients on HCQ and the relatively low incidence of retinopathy. In the United Kingdom, the Royal College of Ophthalmologists, the British Association of Dermatologists, and the British Society for Rheumatology recommend baseline assessment of renal and liver function, inquiry about visual symptoms, and recording...
of near visual acuity with inquiry about visual symptoms at each visit and measurement of visual acuity annually. Buckley et al in the April 2004 guidelines from the United Kingdom for screening suggest that a baseline eye examination and regular ophthalmological screening may not be required in patients taking low (<6.5 mg/kg) doses of HCQ. These guidelines do recommend referral to an ophthalmologist for patients with ocular disease at baseline or for those who develop visual symptoms on treatment. Interestingly the Amsler grid is not included in the annual evaluation recommended for the rheumatology and dermatology clinics but is included in the assessment by ophthalmology.\footnote{Samanta et al reported wide variation among consultant rheumatologists in the United Kingdom and nearly half of surveyed respondents did not assess either baseline visual symptoms or visual acuity.}\footnote{In summary, despite the limitations of the study by Almony et al, TAG may be a more sensitive means for detecting subtle scotomas in patients taking HCQ. The specificity of the TAG however remains to be defined. High risk and low risk features of the individual patient should determine the timing of screening for HCQ retinopathy. Appropriate informed consent, adequate documentation in the medical record, and an appropriate baseline assessment by the prescribing physician are important for medicolegal as well as medical reasons. Because the incidence of HCQ toxicity is extremely low at doses <6.5 mg/kg in asymptomatic and otherwise visually healthy patients, the need and cost effectiveness of baseline and more frequent screening examinations by an ophthalmologist remains debatable. The rationale for examining a patient within the first year of HCQ treatment is to establish a baseline and to document any pretreatment eye disease. The TAG however may be a more sensitive tool for detecting patients in the non-ophthalmology clinic setting who may need a full ophthalmology examination. More frequent screening should be performed in patients taking HCQ with high risk characteristics.} Publications of these recommendations and national guidelines may not ensure compliance however. Samanta et al\footnote{We have followed with interest the discussion ignited by the paper by Reinhard et al\textsuperscript{3} by way of editorial comments from Horton\textsuperscript{2} and Plant.\textsuperscript{3} As co-authors of the paper by Reinhard et al\textsuperscript{3} and collaborators on that study, we have no objections to the data as presented. However, Horton’s interpretation that these data indicate that “no therapeutic intervention … can correct effectively the underlying visual field deficit” after post-chiasmatic injury is not supported by current scientific evidence. On the contrary, a comprehensive and critical review of the literature reveals that there is a sound scientific basis for recommending vision restoration therapy (VRT) for some patients with hemianopia. The Reinhard study\textsuperscript{3} used scanning laser ophthalmoscopy (SLO) to evaluate visual fields before and after a 6 month course of VRT and found no change in the size of the blind field detected by this methodology. An important point well taken by Horton is that rather than relying on the VRT computer based tests alone, it would be “more compelling if visual field improvements could be demonstrated with any standard clinical perimeter.” Although not reported in the Reinhard article, the same patients were also tested by two other perimetric methods: the Tübingen automated perimeter (TAP) and high resolution perimeter (HRP, which is a campsometric visual field test).\textsuperscript{3} We acknowledge that Horton did not have access to this important information which was in press at the time. We believe that not considering these other perimetric data could lead to incorrect conclusions. Even before VRT began, the SLO border was already located significantly closer to the vertical midline than the absolute TAP and HRP borders (fig 1). After VRT, the SLO border was unchanged, but the absolute TAP and HRP borders had significantly shifted, confirming improvement on these measures.\textsuperscript{4} Similar enlargement of the visual field after therapy has been demonstrated on “standard clinical perimetry” by various investigators and laboratories.\textsuperscript{5–9} This apparent discrepancy between the conventional perimetric data and the SLO findings, both at baseline and after therapy, probably reflects the comparatively greater task difficulty of the SLO. It is well known that perimetric performance is task dependent, and the size of the visual field depends critically on stimulus characteristics. In the joint study of the Tübingen-Magdeburg groups\textsuperscript{4}\textsuperscript{3 4} a single near threshold (TAP) or superthreshold bright dot (HRP) was presented on a dark or grey background and the patients had to respond to single stimuli by pressing a button. Contrast these techniques with SLO in which three black dots (a reverse stimulus) were presented on a bright red background which perceptually flickers because it is created by parallel laser lines (the “McKay effect”\textsuperscript{4} see Sabel et al\textsuperscript{4}). Furthermore, patients had to verbally (that is, consciously) report what they were seeing while the experimenter interpreted their verbal reports. Simultaneous stimulus discrimination and detection of negative stimuli on a bright background are probably tasks beyond the abilities of a damaged visual}
Field enlargement. The SLO method appears to be insensitive to relative defects describing areas roughly identical to the SLO border. Among the only four patients who showed a small shift of the blind spot on SLO, none profited from VRT on the SLO, even after VRT, and none of the patients showed stable eccentric fixation on SLO. Secondly, both TAP fixation performance and HRP fixation performance were unchanged after VRT, and both used standard, clinically verified fixation control measures. Additionally, Trauzettel-Klosinski and Reinhard, two of the authors on the study in question, have previously stated that lack of a shift in the blind spot position is a good indicator that fixation is not eccentric. In 12 out of the 16 patients in the SLO study, the blind spot position remained identical after VRT. Among the only four patients who showed a small shift of the blind spot on SLO, none profited from VRT on the other forms of perimeter either. Finally, if eye movements were the cause of visual field expansion, one would expect the entire visual field border to shift. In most patients this is not what is seen. A dramatic example of this is the recently reported selective border shift only within the region of an attention cue. Or take the patient shown in figure 1, in which the visual field defect shrank by shifting of the horizontal border without affecting the vertical border, and the deficit next to the fixation spot was unchanged. If eye movement artefacts had occurred, the reverse would be expected: a shift of the vertical border and no change in the horizontal border. Such border dynamics are incompatible with eye movement artefacts.

Horton is concerned that VRT improvements may simply be a result of placebo effects. However, the study by Kasten et al. described two independent clinical trials in which the placebo effect was controlled for by a randomised, placebo controlled trial and showed that the placebo treatment had no effect in the post-chiasmatic group and only a small effect in the optic nerve group. In this study and in others, patients also reported subjective benefits after VRT, including improved visual function in reading, navigation, and confidence. We agree it is essential to further investigate VRT effects on standardised functional measures of visual performance on everyday life tasks in addition to just perimetry.

There is increasing evidence supported by controlled clinical trials and functional neuroimaging that neuroplasticity is active in many regions of the brain. Training paradigms are now standard in the field of rehabilitation medicine. They are not limited to locomotion therapy, but well established in other functional domains as well (for example, cognitive therapy, memory therapy, speech therapy, auditory therapy, etc). There is no reason why the visual system should be the great exception from all other functional systems of the brain. After all, normal adult subjects are capable of perceptual learning, and there is an entire body of evidence on activity dependent use and neuroplasticity, such as studies on adult receptive field expansions following retinal or brain lesions. We also should remember that the visual system is not purely “sensory.” It utilises many cognitive mechanisms as seen, for example, in the phenomenon of physiological blind spot “filling in” and in the many other mechanisms that contribute to visual perception such as lateral interactions and contour integration.

The precise mechanisms of visual neuroplasticity in the human are not yet defined. Horton believes that in patients with complete hemianopia there is “no fringe of injured but salvageable tissue.” This assumption may be true in some patients, but most patients actually have incomplete hemianopia where...
residual neurons survive within or near the damaged zones (“relative defects”). Even patients with “complete” V1 damage have some preserved visual functions. For example, patients can show non-conscious visual responses (blind sight) which are mediated either by surviving primary cortical afferents and islands of residual vision or by undamaged projections via the colliculus and pulvinar. This latter pathway has most recently been discovered to relay attention relevant information to the eye movement control system and attentional networks are now known to contribute to VRT induced recovery. There is yet another pathway bypassing V1 altogether, as elegantly described by Hortons group: a direct projection from lateral geniculate neurons to the motion sensitive area MT (V5). Thus, there are apparently multiple pathways whereby visual information can reach higher cortical regions without involving V1. Whether or not such pathways have a role in VRT induced visual field enlargements is currently not known, but the search for neurobiological mechanisms of vision restoration deserves further study.

Sensational support of or enthusiastic opposition to a viable technique can only be justified after a meticulous analysis of the complete data in order to enhance scientific discourse. It is true that VRT does not assist all patients. Predictors of recovery have not been completely defined, except that the size of the relative defect tends to correlate with recovery. VRT has now been applied in over 700 patients with confirmation of its effectiveness from several independent studies and laboratories. The FDA has cleared VRT to be offered in the United States and has done so in recognition of the results from the Tübingen-Magdeburg trial. Several clinical centres throughout the United States are now beginning to observe similar improvements with their first patients, confirming the approach to be helpful to patients. Clearly, the relation of objective and subjective visual function after VRT needs further clarification and the role of eye movement compensation in individual hemianopic patients is of interest. However, many hemianopic patients, especially those with partial deficits, benefit from VRT. The evidence supports the conclusion that some visual improvement is possible.


Authors’ affiliations
B A Sabel, S Kenkel, E Kasten, Institute of Medical Psychology, Otto-von-Guericke University of Magdeburg, Magdeburg, Germany

Correspondence to: Bernhard A Sabel, PhD, Institute of Medical Psychology, Otto-von-Guericke University of Magdeburg, Leipzigerstrasse, 44, 39120 Magdeburg, Germany; bernhard.sabel@medizin.uni-magdeburg.de

REFERENCES
The gap between ophthalmology in parts of Africa and more developed countries remains large, and … is growing

The ECWA Eye Hospital in Kano, Nigeria, is a mission hospital started by Dr Hursch, an American ophthalmologist, in the early 1940s. Although there are no surviving records from the time of Dr Hursch, I would venture to say that his practice of ophthalmology in Nigeria was not much different from his practice in America. Since the cutting-edge tools of his day were loupes, and a small set of instruments, those items could easily be purchased, transported, and maintained in the setting of a developing country. Now, 60 years later, the situation is very different.

The eye hospital in Kano remains a bright spot in west Africa for surgery and treatment of eye diseases, and gives invaluable surgical experience to ophthalmologists in training. However, when I arrived in Kano in 2003, I expected that my practice of ophthalmology would be very different from what I was used to in America, and I was not disappointed.

Consider the differences. Just a few years ago in America, I attended a seminar about improving outcomes of cataract surgery. One presenter boasted (rightfully so!) about his accurate selection of IOL (intraocular lens) power within plus or minus 0.25 dioptres, 100% of the time for a large series of patients. He did this by meticulous keratometry, immersion A-scans, and use of a third generation software package. In Africa, there are still many ophthalmologists struggling to convert to ECCE (extracapsular cataract extraction) surgery from ICCE (intra-capsular cataract extraction). Many do not have operating microscopes, and IOLs are hard to come by because of cost and difficulties in importing. For those who do have access to operating microscopes and IOLs, a “standard” IOL power is most often used, since even fewer ophthalmologists have keratometers or A-scans. Couching of cataracts is still practised by traditional healers, even in large urban centres. The treatment of glaucoma in developed countries is aided by an ever increasing armamentarium of medications, optic nerve head analysers, computerised visual field machines, seton implants, and antifibrotic agents. In Africa, most ophthalmologists’ diagnostic tools are limited to Schiotz tonometers and direct ophthalmoscopes. Treatment for glaucoma is also simplified since timolol and pilocarpine are the only drugs readily available, so trabeculectomy is often done earlier. We will skip the comparisons for retina and refractive surgery where the disparities are even greater.

An important factor in this widening gap is the information explosion and rapid pace of technology in the more developed countries. If you are reading this, you likely have access to dozens of specialty and subspecialty journals. When looking back at how cataract surgery has changed just in the past 15 years, the differences are amazing.

Unfortunately, for ophthalmologists in the lesser developed countries, the ability to keep pace with the information explosion is hampered by a number of problems including the relatively high cost of journal subscriptions, and inadequate postal services. Those who do receive journals will find it difficult to implement the new technology and products because of the high costs, and the challenges of importation.

The gap is growing not simply because of the rapid pace of the more developed countries, but also because of myriad complicated problems in poorer countries. Widespread poverty, poor education systems, governmental corruption, AIDS, and inadequate medical training programmes, because of lack of resources and supervision, all contribute to “holding back” the pace of ophthalmic care.

Of course these generalisations do not always hold true. There are places where state of the art ophthalmology is practised in sub-Saharan Africa outside of South Africa, but those places are uncommon. For the majority of Africans, the ophthalmic care received is very different from what we are accustomed to in the more developed countries.

One interesting aspect of the gap is that it goes both ways. Not only are Africans affected by the gap, but ophthalmologists trained in the more developed countries who wish to practice in the less developed parts of Africa are also affected by it. I was fortunate that when I did my ophthalmology training I was taught standard ECCE as well as phacoemulsification surgery. However, currently, many ophthalmology training programmes in America teach only phacoemulsification surgery. If one of those newly trained ophthalmologists wished to practise in Africa, he or she would need additional training. This too may contribute to the widening gap as fewer ophthalmologists will be qualified to practise in developing countries, and fewer will be willing to take a “step backward” in their field.

When referring to the gap, I do not mean to imply that practice in Africa has all the negative aspects. There are several features of practice in the lesser developed parts of Africa that are superior to practice in developed countries. At my workplace in Africa I can practise ophthalmology without many of the bureaucratic headaches we have in more developed countries. Chart documentation can be brief and to the point with no worry about insurance documentation requirements, and much less concern about liability. We are forced to use only technology that is cost effective, and there is little pressure to adopt expensive new technologies with dubious clinical benefit.

There are many individuals, non-governmental organisations, and international health organisations that are working to narrow the negative aspects of the gap. Pervasive availability and usage of the internet may narrow the gap in the information explosion. Low cost educational materials provided by the American Academy of Ophthalmology have been very helpful for training ophthalmologists overseas. “Twinning” is an excellent method whereby collaborations between institutes in developed countries and lesser developed countries occur. Such collaborations can be mutually beneficial, and lead to practice enhancements on both sides.1

However, the gap between ophthalmology in parts of Africa and more developed countries remains large, and in my opinion is growing. We must do more to narrow the gap, and to build bridges to our ophthalmology colleagues, and patients on the other side. There are positive and negative aspects to practice on both sides of the gap, and we would all do well to “mind the gap.”


www.bjophthalmol.com

REFERENCE


www.bjophthalmol.com
Trachoma

How to assess the prevalence of trachoma

H R Wright, H Vu, H R Taylor

TRA for intervention in higher prevalence areas, ASTRA for low prevalence areas

Trachoma is the world’s leading cause of infectious blindness, an estimated 84 million people have active trachoma and 7.6 million have trachomatous trichiasis. It is a disease of poor personal and community hygiene, affecting those living in the poorest conditions, and disappears as living conditions improve. Repeated or persistent infection with the obligate intracellular bacteria Chlamydia trachomatis results in the clinical syndrome of blinding trachoma. Trachoma progresses from inflammation of the upper tarsal conjunctiva to scarring; distortion of the eyelid causes trichiasis and eventual loss of vision secondary to corneal opacity after which blindness is essentially irreversible. The SAFE strategy developed by the World Health Organization (WHO) is effective in controlling blinding trachoma. It targets trachoma intervention at various stages of the cycle of disease: Surgery for trichiasis, Antibiotics for active trachoma, Facial cleanliness, and Environmental improvements. However, simple, reliable, and cost effective systems are needed to identify populations at risk of the blinding complications of trachoma and to assess the effectiveness of trachoma intervention programmes.

METHODS TO ESTIMATE TRACHOMA PREVALENCE

Population based prevalence surveys are the gold standard for estimating the prevalence of active trachoma and trachomatous trichiasis within a community. They have proved the mainstay of targeting and monitoring trachoma intervention; however, they are expensive, time consuming and may utilise resources that could be better spent on intervention programmes. The WHO has published guidelines advising how such a survey can be carried out in order to obtain a good random sample and provide accurate data. However, such surveys are relatively weak at distinguishing between a low level of trachoma and the absence of trachoma unless they have a very large sample size (Figs 1 and 2). This is an important weakness in certifying that an area is free of disease.

Trachoma rapid assessment (TRA) developed by the WHO attempts to quickly, cheaply, and efficiently obtain the information needed to identify and prioritise areas for intervention programmes. It uses a two phase sampling technique to optimally bias the sample to the “worst places” within those communities most likely to have trachoma. At-risk communities are selected from within a region on the basis of existing trachoma information and known socioeconomic conditions. For this reason it can be confidently stated that if trachoma is not found in the “worst areas” it is most unlikely to be found anywhere else within that region. Unfortunately, some have tried to use data from TRA surveys to give prevalence estimates. TRA was explicitly designed not to yield prevalence data as it selects an “optimally biased” sample in order to detect trachoma if present.

Lot quality assurance sampling (LQAS) has also been trialled for the rapid assessment of trachoma. It has long been used in manufacturing and more recently by public health services, predominantly to evaluate service delivery particularly with respect to vaccination coverage. When used as a tool for the rapid assessment of trachoma prevalence the technique has been referred to as asymmetrical sampling trachoma rapid assessment (ASTRA). Children are examined until either a predetermined number of cases with active disease are identified (high prevalence) or a total of 50 children are sampled without the cut-off point being reached (low prevalence). Communities are categorised as low or high prevalence and the values of these categories can be adjusted by selecting the cut-off point at which sampling stops.

BRIEF SUMMARY OF FIELD TRIALS OF TRA AND ASTRA

Results of several TRA field tests have been published some of which have compared TRA with prevalence survey results. They suggest that TRA is reasonably accurate in prioritising communities with higher levels of active trachoma. TRA did less well ranking communities with a low prevalence, although this is relatively less important as these communities were almost always assigned a low priority ranking. All studies reported that TRA was quicker and cheaper than a prevalence study. Two studies reported that there was an overemphasis on risk factor scores.

There is one published report of the effectiveness of ASTRA. The threshold was set at 14 and a maximum of 50 children are sampled without the cut-off point being reached. For this survey type the technique has been referred to as asymmetrical sampling trachoma rapid assessment (ASTRA). Children are examined until either a predetermined number of cases with active disease are identified (high prevalence) or a total of 50 children are sampled without the cut-off point being reached (low prevalence). Communities are categorised as low or high prevalence and the values of these categories can be adjusted by selecting the cut-off point at which sampling stops.

**Figure 1** The 95% confidence interval (CI) for each survey method when the observed prevalence is 5% and 0%. Circles/squares show the observed prevalence, bars show 95% CI limits (actual value in parentheses), and arrows signify that there is no limit in this direction for this survey type.
children aged 2–5 were identified for examination. They were able to accurately identify a community with a prevalence of ≤20% with a sensitivity of 94% and a prevalence of ≥40% with 95% sensitivity.

WHICH METHOD IS MOST APPROPRIATE?
According to the WHO guidelines a community should receive mass antibiotic treatment when the prevalence of active trachoma is more than 10% among 1–9 year old children. Treatment should continue for at least 3 years and should not stop until the prevalence is below 5%. Prevalence surveys remain the gold standard and are necessary to monitor intervention programmes, but TRA and ASTRA have an important role. Deciding which survey method to use must take into account the aim of the survey, the anticipated trachoma prevalence, and any important local concerns.

When assessing an area to determine if and where an intervention programme should be implemented TRA provides the quickest and surest way of ascertaining whether trachoma exists or not. It will also assist in prioritising or ranking communities or areas for intervention. ASTRA could also be used but it may miss pockets of disease.

To monitor the progress of an ongoing trachoma intervention programme, ASTRA can give a broad brush guide of the prevalence of disease. However, the selection of some “sentinel” communities for repeat prevalence assessment may be preferred by some.

To certify the elimination of trachoma one would again turn to the targeted TRA method or else use a prevalence survey with a very large sample size.

CONCLUSION
When deciding on which survey technique to use it is important to consider the aim of the survey. TRA can accurately and rapidly prioritise communities for intervention in higher prevalence areas; however, ASTRA may be better in low prevalence areas. Once a community has been identified for intervention a prevalence survey, or possibly ASTRA could be undertaken to allow programme monitoring. Finally, in order to certify that a region is clear of trachoma TRA is the most efficient method.

ACKNOWLEDGEMENTS
This research at the Vision Cooperative Research Centre was partly supported by the Australian Federal Government through the Cooperative Research Centres Program.


Authors’ affiliations
H R Wright, H Vu, H R Taylor, Centre for Eye Research Australia (CERA), Vision CRC, Victoria, Australia

Correspondence to: Dr Heathcote R Wright, CERA, Locked Bag 8, East Melbourne, Vic 8002, Australia; h.wright2@pgrad.unimelb.edu.au

Competing interests: none.

REFERENCES
Mirror, mirror, on the wall...

H as this happened to you? In the darkness, on a lonely country road, your headlights play across a pair of bright green, almost iridescent, spots of light; they seem to float eerily across the road without support. These furtive spots seem to move and blink, clearly alive. Eyeshine. It is all you see of the creature, as the rest of the body seems to disappear into the darkness that surrounds it. But, what exactly is eyeshine, and why did it evolve?

The *tapetum lucidum* (Latin, carpet shining) is a reflective structure found in the eyes of many diverse creatures and represents convergent ocular evolution solely for maximising photon capture. Surprisingly, the techniques for the production of these reflective mechanisms are variable, and much like the crystalline lens, seem to be drawn from whatever materials the evolutionary process found at hand.

Guanine crystals, for example, provide biological reflection and support camouflage by making a fish glisten and gleam, and hence appear invisible or at least present confusing reflections to a predator. Although we can never know for sure, this coating probably appeared very early in the development of fish as a protective mechanism, perhaps as early as the Silurian (500–450 million years ago) and certainly by the Devonian period (410–360 million years ago).

Many fish, then, must have co-opted this protein to be a biological reflective coating directly beneath the photoreceptors in the choroid, and it remains a common, and effective, mechanism among fish. Other fish such as carp, eels, lantern fish, have retinal tapeta that include reflecting materials and pigmented compounds such as pteridine. Still other fish have a tapetum cellulosum, located in the choroid, which is not seen again phylogenetically until certain mammals.

Arthropods became terrestrial during the Devonian period, and among those creatures, insects became both predators and prey and they devised ways to extend their lifestyles into the darkness. Some arthropods such as spiders use guanine for tapeta, as this protein is probably very old. Moths and butterflies found different, but no less creative, mechanisms for light reflection.

Insects deliver oxygen to ocular tissues through a series of tubes branching directly off the trachea. As this Roman aqueduct-like system of oxygen delivery grows smaller as it approaches the internal structures of the eyes, the periodicity of the chambers directly beneath the ommatidia has evolved a separation distance exactly coincident with a quarter the wavelength of light, at least in some species. As light enters the ommatidium, striking each of the 40 or so layers of these tracheal branches or tracheoles, a bit of light is reflected from each surface. With the periodicity of these surfaces at a quarter of the wavelength of light, constructive interference increases and intensifies the reflection until perhaps as much as 90–100% (at least theoretically) of the incident light is reflected back through each photoreceptive element in the ommatidium. The light, once reflected, continues back through the photoreceptive element and exits the eye on almost the identical path it entered. So, even a small torch will illuminate a moth or a spider, with two small red gleaming dots of light looking back at you.

As previously discussed (*BJO* November cover, 2004) tetrapods also ventured into a terrestrial lifestyle in the Devonian period, although curiously enough, the tapetum probably did not accompany these creatures since neither frogs nor salamanders have it. The vertebrate tapetum does not appear phylogenetically again until reptiles and mammals. As you might imagine in convergent evolution, the mechanisms were not the same (Schwab IR et al, *Trans Am Ophthalmol 2002;100*:187–200).

Crocodiles have a retinal tapetum with the reflective coating immediately beneath and within the outer retina, and specifically not within the choroid. Members of other reptilian clades such as the tuatara (*BJO* March cover, 2005) do not have a tapetum, whatsoever, illustrating that it was not a universal trait even among nocturnal animals.

Later, mammals, especially the hoofed mammals and their predators, the major carnivores (dogs and cats), developed tapeta. These tapeta, though, are choroidal and can be divided into pigmented and non-pigmented. The pigmented tapeta have used different light scattering pigments such as lipids, astaxanthin, and melanoid compounds to create a mosaic carpet coloured with brilliant reds and blues. The non-pigmented choroidal tapeta can be further subdivided into fibrous and cellular. The tapetum cellulosum is composed of reflecting cells stacked in depth, like tilework. The tapetum fibrosum (the Nilgiri tahr, a member of the goat family, is the cover image and has a tapetum fibrosum) is acellular and composed of stacks of densely packed collagen fibrils. Each type has evolved seemingly in tandem and whose mechanism is constructive interference as described above.

The tapetum has evolved to maximise photon capture by reflecting much of the light that traverses the photoreceptive element directly above it, but not without some sacrifice. The reflection can scatter to adjacent photoreceptive elements and, depending on shielding of adjacent photopigment may inadvertently cause that receptor to fire. This would blur an image and degrade acuity. So, most predators, since they require better acuity, have protected adjacent photoreceptors with pigment sheaths, or in the case of invertebrates, with steep walled ommatidia that never reach the angle of reflection.

These mirrors, then, are biological oddities cobbled together as necessity dictates and reflect the creativity of random evolutionary mechanisms and unfathomable lengths of time.

I R Schwab
University of California, Davis, Sacramento, CA, USA; irschwab@ucdavis.edu

Cover image of *Hemitragus Jyleucus* (Nilgiri tahr) by I R Schwab; fundus photographs by Ned Buyukmihci, VMD

Cover: Nilgiri tahr on left and image of goat fundus on right.
SCIENTIFIC REPORT

Limbal epithelial crypts: a novel anatomical structure and a putative limbal stem cell niche

H S Dua, V A Shanmuganathan, A O Powell-Richards, P J Tighe, A Joseph

Methods: Systematic serial 5–7 μm sections of human corneoscleral segments obtained from cadaver donors, were examined. The sections were stained with haematoxylin and eosin or toluidine blue. Sections with specific areas of interest were further examined immunohistologically for the corneal epithelial marker cytokeratin 14 and the “stem cell” marker ABCG2 transporter protein.

Results: Distinct anatomical extensions from the peripheral aspect of the limbal palisades were identified. These consist of a solid cord of cells extending peripherally or circumferentially. The cells stained positive for CK14 and ABCG2.

Conclusions: A novel anatomical structure has been identified at the human limbus, which demonstrates characteristics of being a stem cell niche. The authors have termed this structure the limbal epithelial crypt.

Most self renewing tissues are served by stem cells. Stem cells are poorly differentiated, slow cycling cells with a great capacity for clonogenic expansion and error free division. They are self renewing, can proliferate indefinitely, and survive for the duration of the organism in which they reside. Stem cells usually are confined to their “niche,” a specific location within the organ where the microenvironment supports and maintains the “stemness” of stem cells and affords a degree of protection. In solid organs, where cell migration commences at one point and progresses until the cells are shed at a distant point(s), the stem cell niche is usually located at the point of commencement. The key attributes of stem cells are their potency and plasticity—that is, their ability to give rise to multiple cell lineages and to transdifferentiate into totally different cell type(s) when relocated to a novel stem cell niche. At the ocular surface, there is a considerable body of evidence that supports the notion that the corneal epithelial stem cells are located in the palisades of Vogt at the corneoscleral limbus. However, neither stem cells nor a specific niche for stem cells have been identified at the limbus, which is in part related to the lack of a specific stem cell marker. Most defined stem cell niches are located deeper in the tissue than their differentiated progeny. We therefore hypothesised that the human limbus must also contain an anatomically defined site that could serve as a niche.

METHODS

Corneoscleral rims from a total of five donors were analysed. Four of these were from fresh donors and the fifth from an organ cultured cornea. Donor ages were between 17 and 75 years. Segments of the rim were embedded in either optimum cutting temperature (OCT) compound (Dako Cytomation, Cambridgeshire, UK) and frozen in liquid nitrogen, fixed in formalin, and embedded in paraffin or fixed in glutaraldehyde and embedded in resin.

The tissue blocks were then cut into serial 5–7 μm sections. These were stained with haematoxylin and eosin and those fixed in glutaraldehyde were stained with toluidine blue. Every section was examined by light microscopy using a Nikon Labphot-2 microscope.

Immunohistochemistry was carried out using antibodies to CK14 (clone LL002, Serotec, Oxford, UK) and a recently described stem cell marker (side population cells) ABCG2 transporter (clone BXP-21, Oxford Biotechnology Ltd, Oxford, UK). A two step horseradish peroxidase method using diaminobenzidine (DAB) as substrate was employed.

Images of serial sections of an area of interest from one rim were later reconstructed to produce a three dimensional image using the Olympus analySIS pro software (Olympus Biosystems, Olympus Optical Co UK Ltd).

RESULTS

A novel and unique anatomical structure was identified at the limbus of all specimen studied. We termed the structure the limbal epithelial crypt (LEC) (figs 1 and 2). LECs extended from the peripheral aspect of the undersurface of an interpalisade rete ridge and extended either radially into the conjunctival stroma parallel to the palisade or circumferentially along the limbus at right angles to the palisade. The structure was widest at its origin from the rete ridge and gradually tapered to a narrow extension at its termination (figs 1 and 3). The length measured up to 120 μm. There were an estimated six per specimen of the human limbus.

On immunohistochemistry CK 14 staining was observed in all cells of the LEC and matched that of the more superficial cells (fig 3A). ABCG2 staining was maximum in the cells packed in the LEC and extended from the tail of the LEC towards the basal layer of the interpalisade rete ridge (fig 3B). The intensity of the basal cell staining for ABCG2 decreased more rapidly along the conjunctival basal layer than the limbal basal layer of cells. Some suprabasal cells showed membranous staining for this marker.

DISCUSSION

The limbus is an anatomical and functional unit located circumferentially along the periphery of the cornea at its junction with the sclera and the conjunctiva. A large body of circumstantial evidence, both clinical and basic, supports the view that corneal epithelial stem cells are located at the limbus. For instance, corneal epithelial regeneration and

Abbreviations: CK, cytokeratin; DAB, diaminobenzidine; LEC, limbal epithelial crypts; OCT, optimum cutting temperature; TAC, transient amplifying cells
wound healing occurs by a distinct centripetal migration of cells from the limbus. Limbal epithelial wounds heal by a characteristic circumferential migration of epithelial cells from any remaining intact epithelium. Limbal epithelial healing always precedes closure of central epithelial defects when both occur simultaneously. Disease or destruction of the corneoscleral limbus leads to ingress of conjunctiva derived cells, including goblet cells, and blood vessels onto the normally avascular corneal surface affecting its optical properties and leading to visual impairment or blindness. Surgical transplantation of autologous or homologous limbal tissue restores corneal epithelial structure and function. Despite this compelling clinical evidence, the identification of a specific marker for limbal stem cells or their niche remains elusive.

In 1971, the pericorneal palisades were first proposed to represent the source for renewal of corneal epithelial cells. Several laboratory studies too have indicated that corneal epithelial stem cells are located at the limbus. Limbal epithelial cells are cytokeratin (CK) 5/14+, CK19+, and CK3/12−. These cells also show staining for vimentin, epidermal

Figure 1 Serial sections stained with haematoxylin and eosin showing how the niche originates from the undersurface of a palisade at the limbus and gradually tapers towards its tail end in the substantia propria. This particular limbal epithelial crypt was oriented circumferentially along the limbus. Magnification ×100.

Figure 2 This is a three dimensional reconstruction, from serial histological sections, of the proposed stem cell niche for corneal epithelial stem cells. In this example the limbal epithelial crypt extends circumferentially along the corneal circumference (arrow).

Figure 3 (A) Immunohistology of a LEC showing positive staining for cytokeratin 14 demonstrating that all cells in the crypt were epithelial in nature (immunoperoxidase, DAB ×400). (B) Immunohistology of a LEC showing positive staining for ABCG2. Note that all crypt cells stain while only basal cells of the epithelium stain with equal intensity to the crypt cells. Some suprabasal cells show membranous staining (immunoperoxidase, DAB ×400).
growth factor receptors, alpha enolase and are connexin 43 negative.\textsuperscript{11,14} Recently a nuclear transcription factor, P63 was proposed for a marker for limbal stem cells\textsuperscript{15} but this was not substantiated by other studies.\textsuperscript{16} Attempts to identify limbal stem cells and their niche by using antibodies to established haematopoietic stem cell markers such as CD34 and CD133 were also unsuccessful.\textsuperscript{16} In a recent fairly extensive immunohistological study of cultured human corneal epithelial cells using various cytokeratin and other markers (P63, integrin beta-1, and epidermal growth factor receptor) Kim et al\textsuperscript{17} did not demonstrate any single or combination of markers to identify stem cells. They did notice slow cycling cells which retained BrdU label indicating that some of the cells possessed this particular stem cell characteristic.

An ATP binding cassette transporter protein, ABCG2, is believed to be a marker of a side population cells that have the ability to efflux Hoechst 33342 dye.\textsuperscript{18} In a number of different organ systems, side population cells as determined by ABCG2 staining, are believed to contain, but not exclusively represent, stem cells.\textsuperscript{19–23} Recently Chen et al\textsuperscript{24} demonstrated that ABCG2 is primarily expressed in limbal basal cells and as such may constitute part of a stem cell phenotype. Similarly Watanabe et al\textsuperscript{25} have also shown that a portion of limbal epithelial basal cells expressed ABCG2 and could represent the putative corneal epithelial stem cells.

Stem cells are known to be located in identifiable niches, which in self renewing tissues, are generally anatomically defined sites.\textsuperscript{26} The bulge region of the hair follicle and the crypt of an intestinal villus are two such examples.\textsuperscript{27} The microenvironment, in the midst of which the stem cells are located, contributes to the development and maintenance of the various unique features that characterise a stem cell. This microenvironment is made up of extracellular matrix components, other resident cells, and the products and signals they release. Collectively they constitute the niche. The immediate progeny of stem cells that step outside the niche have the potential to proliferate rapidly and provide the capacity for rapid expansion of the cell numbers in case of need. These cells are referred to transient amplifying cells (TAC). Several of the markers mentioned above differentiate limbal basal cells from peripheral corneal basal cells. This led to the notion that the entire limbal basal cell population may serve as stem cells. The identification of LEC in this study presents the limbal niche concept in a new light. If the LEC were to act as a repository of stem cells then the basal cells of the limbus and peripheral cornea would serve the function of TAC. This would also explain why several of the characteristics of the basal cells of the limbus are similar to those of the peripheral cornea and why attempts to identify differences between these two sets of basal cells, with a view to mark limbal stem cells have not proved fruitful.

The LEC are anatomically well defined structures and are located deeper in the substantia propria of the limbus providing both protection and a microenvironment of extracellular matrix with its multitude of resident cells. All cells within the LEC are epithelial in nature as demonstrated by their CK14 staining. ABCG2 staining was densest within the LEC cell population and extended along the basal cells of the limbus more than along the basal cells of the adjacent conjunctiva. If the cells within the LEC were at the bottom of the stem cell escator and the basal epithelial cells at the top then such a distribution would be natural and expected. Although this in itself is not conclusive proof that the LEC cells are stem cells it does indicate that the LEC have the hallmarks of a “niche.” As ABCG2 is not a specific stain for stem cells in the limbus or in any other organ, it is unlikely that all ABCG2 staining cells represent stem cells. In the light of the existing evidence from other organs it would appear that stem cells are contained within this particular population of cells, which could represent stem cells and their immediate progeny. This would also explain positive staining along the limbal basal epithelium and the larger proportion of cells staining positive for ABCG2 than could be accounted for by stem cells alone. Further studies on cell cycling within LEC and the proliferative potential of LEC cells will help in determining their stem cell nature.

ACKNOWLEDGEMENTS

This work was funded in part by the Charles Hayward Foundation and The Henry Smith Charity, and the Royal Blind Asylum and School/Scottish National Institution for the War Blinded, The Royal College of Surgeons of Edinburgh.

Authors’ affiliations

H S Dua, V A Shanmuganathan, A O Powell-Richards, P J Tighe, A Joseph, The Larry A Donoso Laboratory for Eye Research, Division of Ophthalmology and Visual Sciences, University of Nottingham, Nottingham, UK

This work was presented in part at 8th Nottingham Eye Symposium, January 2004 and at the Oxford Ophthalmic Congress July 2004.

Correspondence to: Professor Harminder S Dua, Division of Ophthalmology and Visual Sciences, B Floor, Eye Ear Nose and Throat Centre, University Hospital, Nottingham NG7 2UH, UK, harminder.dua@nottingham.ac.uk

Accepted for publication 2 August 2004

REFERENCES


**Video reports**

To view the video reports in full visit our website www.bjophthalmol.com and click on the link to the video reports.
- Removal of INTACS: Stepped surgical complexity demonstrated with three cases. L Ilari, J C McAlister, D S Gartry
- The Nuclear Slide: A novel approach for unleashing the potential of the hydrodissection wave. A Naseri
- Giant pleomorphic adenoma of the lacrimal gland: pre- and post-operative function. A Jain, V I Nehru, U N Saikia, C E E Reddy
- Limbal-sparing lamellar keratoplasty. S L Watson, S Rauz, J Dart
- Bilateral Abducens Neuromyotonia. L H Ospina, N Aui-aree, D P Anderson
- Light to dark physiological variation in irido-trabecular angle width. G M Gazzard, P J Foster, D S Friedman, P T Khaw, S K L Seah

Video Suite: Triamcinolone-assisted vitrectomy
- Triamcinolone-assisted removal of the posterior hyaloid to repair retinal detachment due to macular hole in high myopia. A Ueno, H Enaida, Y Hata, T Nakamura, T Hisatomi, K Fujisawa, T Kubota, T Sakamoto, T Ishibashi
- Triamcinolone acetonide-assisted Epiretinal Membrane Peeling. S D M Chen, C K Patel
- A suture technique to manage a case of severe early flap displacement after laser in situ keratomileusis. L Spadea, P Pantaleoni, G Bianco
- Reconstruction of the Ocular Surface in LOGIC Syndrome. E Moore, V Kumar, J R Ainsworth, S Shah
- Laser Photocoagulation for Posterior Segment Intraocular Parasites. T Prabriputaloong, S Asawaphureekorn
- Feeder Vessel Treatment with High Speed ICG Angiography. D Stanescu-Segall, G Coscas, F Coscas, G Soubbrane
- Endoscopy to aid anterior segment surgery. J E Moore, A Sharm
- Penetrating ocular injury due to a fish hook: Surgical removal. S D M Chen, D Chiu, C K Patel
- Retinal Ganglion Cell Axon Response to Guidance Molecules. S F Oster and D W Sretavan
- Marin-Amat Syndrome. A Jogiya, C Sandy
- Excision of subcutaneous Dirofilariaasis of the eyelid. D Mallick, T P Ittyerah
- Thixotropy: a novel explanation for the cause of lagophthalmos after peripheral facial nerve palsy. M Aramideh, J H T M Koelman, P P Devriese, F VanderWad, J D Speelman
- Surgical revision of leaking filtering blebs with an autologous conjunctival graft. K Taherian, A Azauro-Blanco
- Dipetalonema Reconditum in the human eye. T Huynh, J Thean, R Maini
Anti-TNF-α therapy for sight threatening uveitis
E W Lindstedt, G S Baarsma, R W A M Kuijpers, P M van Hagen

Aim: To describe the effect of additional treatment with anti-TNF-α therapy in a case series of 13 patients with serious sight threatening uveitis.

Methods: 13 patients with serious sight threatening uveitis were included, of whom six had Behçet’s disease, five had idiopathic posterior uveitis, one had sarcoidosis, and one birdshot retinochoroiditis. Onset and course of ocular inflammation, inflammatory signs, and visual acuity were assessed. Patients were treated with 200 mg (approximately 3 mg/kg) infliximab infusion. Repeat infusions were given based on clinical response.

Results: Infliximab treatment resulted in an effective suppression of ocular inflammation in all patients. In patients with non-Behçet’s disease uveitis visual acuity in six out of eight improved or was stable. In patients with Behçet’s disease visual acuity in five out of six improved or was stable.

Conclusion: Anti-TNF-α treatment may be of value in the treatment of uveitis, and in patients with Behçet’s disease, leading to suppression of ocular inflammation, vasculitis, and improvement of vision in the majority. Based on these results a controlled masked study is warranted.

The cytokine tumour necrosis factor alpha (TNF-α) is an important factor in the pathogenesis of uveitis. In animal experiments TNF-α has been detected in an early phase of endotoxin induced uveitis in rats. Increased levels of inflammatory cytokines such as TNF-α have been implicated in the pathogenesis of experimental autoimmune uveitis (EAU) in rats and in mice. This cytokine may induce the expression of chemokines, adhesion molecules, and other cytokines involved in the prolongation of inflammation. Inhibition of TNF-α activity results in suppression of Th1 effector mechanism, suppresses activation of infiltrating macrophages, and prevents tissue destruction in EAU. Greiner et al showed that anti-TNF-α therapy modulates peripheral blood T cells in patients with posterior segment intraocular inflammation, which contributes to the recovery of visual function.

In patients with uveitis including Behçet’s disease, TNF-α levels are raised in serum and in aqueous humour. Because of its pivotal role in inflammation, blockade of TNF-α activity may be effective in the treatment of uveitis. Anti-TNF-α therapies were originally established in rheumatoid arthritis. Infliximab (Remicade, Schering-Plough) is a chimeric IgG monoclonal antibody directed against TNF-α. It binds with high affinity to the soluble and transmembrane forms of TNF. After intravenous administration the half life of infliximab is about 10 days and its biological effect persists for up to 2 months. Because of its impressive anti-inflammatory effects anti-TNF-α therapy has been successfully used in other inflammatory diseases like Crohn’s disease, sarcoidosis, ankylosing spondylitis, and psoriatic arthritis. In recent articles favourable results were reported in the treatment of patients with Behçet’s disease and also endogenous uveitis. However, serious side effects have also been reported, including exacerbation of demyelinating disease, bilateral anterior optic neuropathy, tuberculosis, histoplasmosis, and even sudden death in patients with cardiac insufficiency. These side effects are rare and have to be compared with those of other immunosuppressive and cytotoxic agents which are used to treat these patients. Till the end of August 2003 about 493 000 patients worldwide were treated with anti-TNF-α therapy (data retrieved from Centocor). We report our experience of infliximab treatment in a case series of 13 patients with sight threatening uveitis refractory to conventional immunosuppressive therapy. Anti-TNF-α therapy may be included in the treatment of sight threatening uveitis.

METHODS
We investigated whether additional treatment with anti-TNF-α therapy had a beneficial effect in 13 patients with serious sight threatening uveitis. Patients were selected because they deteriorated despite treatment with other immunosuppressive drugs such as corticosteroids, cyclosporine, methotrexate and interferon alfa or had serious side effects on these treatments (table 1). Topical non-steroidal anti-inflammatory drugs and steroids were used in all patients.

Treatment
Six of the 13 patients with longstanding Behçet’s disease, fulfilling the international study group criteria were treated. The patient characteristics are summarised in table 1. All patients with Behçet’s disease had a history of recurrent sight threatening episodes of uveitis. Five of these patients had only one functional eye. The other eye had a maximal visual acuity of counting fingers or less because of optic atrophy (one), macular lesions (one), phthisis bulbi (one), enucleation (one), or amblyopia (one). Five patients had idiopathic posterior uveitis (two patients with one functional eye), one patient had sarcoidosis, and one birdshot retinochoroiditis (one functional eye). Before the treatment all patients had an extensive physical examination with special attention to tuberculosis, infections, malignancies, cardiac insufficiency, and signs of lupus erythematosus. Routine laboratory investigations were performed (haematogram, kidney, and liver function tests) at baseline and during follow up.

Treatment protocol
After verbal informed consent we administered 200 mg of infliximab (approximately 3 mg/kg) intravenously in an outpatient setting. A series of 1–12 infusions were given based on clinical response. In case of relapse of disease anti-TNF-α therapy was restarted. This means a restart at different intervals for each patient. Initially infliximab was given as additional treatment. Ophthalmological assessment was performed, including Snellen visual acuity, intraocular pressure, visual field, slit lamp examination, and fluorescein angiography.

Abbreviations: EAU, experimental autoimmune uveitis; MTX, methotrexate; TNF-α, tumour necrosis factor alpha
pressure, slit lamp biomicroscopy, and indirect ophthalmoscopy of the posterior segment. Examinations were performed on day 0 and during follow up for at least 2 years. Inflammatory activity of the anterior and posterior chamber was scored according to Kimura et al. Presence of retinal vasculitis (choroidal lesions, retinal lesions, vascular sheathing or macular lesions) was scored as well, either as vasculitis (choroidal lesions, retinal lesions, vascular sheathing or macular lesions) was scored as well, either as vasculitis (choroidal lesions, retinal lesions, vascular sheathing or macular lesions) was scored as well, either + or − or were described (table 2).

An effective suppression of ocular inflammation—that is, quiescence of inflammation in the anterior chamber and/or diminishing of vitreous cell and/or disappearance of vasculitis, along with an improvement or stabilisation of visual acuity together with a clinical improvement both objectively and subjectively reflects successful treatment. We regarded an improvement in VA of more than two decimal points as clinically significant.

**RESULTS**
The effects of therapy were assessed in two ways.

**Reduction of inflammation**
As shown in table 2 the initial administration of anti-TNF-α therapy resulted in a suppression of ocular inflammation (that is, quiescence of inflammation in the anterior chamber, diminishing of vitreous cell, or disappearance of vasculitis) and clinical improvement in all patients, especially in patients with Behçet’s disease. Patients with uveitis and Behçet’s disease responded in less than 7 days to 3 weeks after infusion with infliximab, whereas patients with serious uveitis without Behçet’s disease responded variably, between 6 days to 2 months. We observed that remission was accomplished in patients with Behçet’s disease after 1–3 infusions. The majority of these patients could be controlled subsequently on conventional immunosuppressive therapy only. Concurrent improvement of longstanding orogenital ulcerations occurred within days after the infusion of infliximab in all patients with Behçet’s disease. Furthermore, non-ocular inflammatory symptoms such as synovitis, thrombophlebitis and gastrointestinal lesions improved dramatically or resolved completely within 1 or 2 weeks after infliximab infusion.

**Effect on visual acuity**
Subjectively, the improvement of visual acuity started within a few days. Table 3 shows the visual acuity in all 13 patients after at least 2 years of follow up, the number of anti-TNF-α infusions along with subsequent co-medication. Three out of six patients with Behçet’s disease—that is, four eyes, had a significant improvement of visual acuity. As has been described in table 3 most eyes had irreversible ocular damage so stable vision in the remaining eyes may indicate some benefit of treatment. Two out of five patients with idiopathic posterior uveitis—that is, two eyes, had a significant improvement of visual acuity, the other eyes were stable (six eyes) or worsened (two eyes, one eye lost light perception). The patients with sarcoidosis and birdshot retinochoroiditis were stable.

The treatment was well tolerated by most patients. In two patients, the therapy was discontinued; in one because of a rash and in the other one because of development of relapse of atopic dermatitis. In both, the skin lesions disappeared after discontinuation of anti-TNF-α therapy.

In patients 1 and 2 infliximab treatment was restarted, in patient 1 because of polyarthritis and in patient 2 because of a severe refractory colitis. In the patients with idiopathic posterior uveitis 1–4 infusions were needed to achieve remission. The ocular inflammatory activity in patients A, C, and E was controlled subsequently with conventional immunosuppression. Patient B had a relapse 2 months after the first three infusions and did not respond well to two more infliximab infusions; he was further treated with steroids to control the uveitis. In patient D treatment was stopped after

---

**Table 1** Patient characteristics and previous treatment

<table>
<thead>
<tr>
<th>Patients</th>
<th>Presentation*</th>
<th>Previous systemic treatment</th>
<th>Duration of disease (years)</th>
<th>Patient</th>
<th>Presentation*</th>
<th>Previous systemic treatment</th>
<th>Duration of disease (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behçet’s disease: n = 6, mean age: 44, range 32–66</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1, M; 38 years, Behçet’s disease</td>
<td>OA + GU, A, TF, BU</td>
<td>Cyclosporine, colchicine, interferon alfa, prednisone</td>
<td>6</td>
<td>Patient 4, M; 56 years, Behçet’s disease</td>
<td>OA + GU, A, SL, BU</td>
<td>Cyclosporine, colchicine, azathioprine</td>
<td>22</td>
</tr>
<tr>
<td>Patient 2, M; 32 years, Behçet’s disease</td>
<td>OA + GU, A, SL, C, BU</td>
<td>Azathioprine, interferon alfa</td>
<td>10</td>
<td>Patient 5, M; 34 years, Behçet’s disease</td>
<td>OA + GU, A BU</td>
<td>Interferon alfa</td>
<td>15</td>
</tr>
<tr>
<td>Patient 3, F; 37 years, Behçet’s disease</td>
<td>OA + GU, A, TF, SL, BU</td>
<td>Cyclosporine, colchicine, interferon alfa</td>
<td>6</td>
<td>Patient 6, M; 66 years, Behçet’s disease</td>
<td>OA + GU</td>
<td>Cyclosporine</td>
<td>7</td>
</tr>
<tr>
<td>Patient A, F; 31 years, idiopathic uveitis</td>
<td>Prednisone, MTX</td>
<td></td>
<td>5</td>
<td>Patient E, F; 38 years, idiopathic uveitis</td>
<td>Prednisone, cyclosporine</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Patient B, M; 29 years, idiopathic uveitis</td>
<td>Cyclosporine, prednisone, interferon alfa</td>
<td></td>
<td>7</td>
<td>Patient F, M; 39 years, sarcoidosis</td>
<td>Prednisone, MTX</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Patient C, F; 62 years, idiopathic uveitis</td>
<td>Prednisone, cyclosporine</td>
<td></td>
<td>2</td>
<td>Patient G, F; 60 years, birdshot</td>
<td>Cyclosporine, prednisone, MTX</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Patient D, M; 20 years, idiopathic uveitis</td>
<td>Octreotide LAR, prednisone</td>
<td></td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


---
two infusions because no effect was observed. This was attributed to the pre-existing destructive retinal fibrosis. Patient F responded very well after the first infusion; unfortunately, he developed a rash after three infusions which forced us to stop the treatment. The ocular inflammation is now under control with conventional immunosuppression. The patient with birdshot retinochoroiditis developed a rash after the first infusion and treatment was

<table>
<thead>
<tr>
<th>Patient</th>
<th>Eye</th>
<th>VA&lt;T=0</th>
<th>VA&lt;T=0+x</th>
<th>AC&lt;T=0</th>
<th>AC&lt;T=0+x</th>
<th>AH&lt;T=0</th>
<th>AH&lt;T=0+x</th>
<th>VC&lt;T=0</th>
<th>VC&lt;T=0+x</th>
<th>F&lt;T=0</th>
<th>F&lt;T=0+x</th>
<th>x [days after infusion]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RE</td>
<td>20/30</td>
<td>20/25</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RE</td>
<td>20/50</td>
<td>20/30</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RE</td>
<td>20/60</td>
<td>20/40</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>0.6</td>
<td>20/25</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>RE</td>
<td>CF</td>
<td>CF</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>20/30</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>RE</td>
<td>20/200</td>
<td>20/100</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>RE</td>
<td>CF</td>
<td>CF</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>RE</td>
<td>20/150</td>
<td>20/80</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>20/200</td>
<td>20/100</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>RE</td>
<td>20/40</td>
<td>20/20</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>CF</td>
<td>20/150</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>RE</td>
<td>20/50</td>
<td>20/40</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>CF</td>
<td>20/40</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>RE</td>
<td>20/400</td>
<td>20/200</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>RE</td>
<td>20/200</td>
<td>20/200</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>20/200</td>
<td>20/200</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>RE</td>
<td>20/40</td>
<td>20/40</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>20/40</td>
<td>20/40</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>RE</td>
<td>20/120</td>
<td>20/60</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>LE</td>
<td>CF</td>
<td>20/200</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

VA, visual acuity according to Snellen equivalent; AH, aqueous haze; F, fundus (presence of vasculitis: 1; no vaculitis: 0); AC, aqueous cell; T, time; VC, vitreous cell; CRVO, central retinal vein occlusion.

$x$: number of days after start of the first treatment when re-examination was performed.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total TNF infusions</th>
<th>VA before start</th>
<th>VA after at least 2 years follow up</th>
<th>Fundus lesions</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>RE: 20/30</td>
<td>RE: 20/20</td>
<td>Macular hole/fibrosis LE</td>
<td>Infliximabs 200 mg iv, prednisone 1 mg/day, prednisone after 3 months ↓ to 10 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: LP+</td>
<td>LE: CF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>RE: 20/50</td>
<td>RE: 20/30</td>
<td>Ischaemic optic atrophy, RE+LE</td>
<td>Infliximabs 200 mg iv, cyclosporine 200 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: LP+</td>
<td>LE: LP+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>RE: 20/60</td>
<td>RE: 20/80</td>
<td>Optic atrophy, RE+LE</td>
<td>Infliximabs 200 mg iv, MTX 3 x/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: 20/30</td>
<td>LE: 20/40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>RE: CF</td>
<td>RE: 20/200</td>
<td>Macular fibrosis LE</td>
<td>Infliximabs 200 mg iv, prednisone 15 mg/day, MTX 12.5 mg/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: 20/30</td>
<td>LE: 20/30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>RE: 20/200</td>
<td>RE: 20/200</td>
<td></td>
<td>Infliximabs 200 mg iv, prednisone 15 mg/day, MTX 12.5 mg/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12</td>
<td>RE: 20/150</td>
<td>RE: 20/40</td>
<td>Macular scarring RE+LE</td>
<td>Infliximabs 200 mg iv, prednisone 10 mg/day, ledertrate 1 x/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: 20/200</td>
<td>LE: 20/100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>RE: 20/40</td>
<td>RE: 20/40</td>
<td></td>
<td>Infliximabs 200 mg iv, prednisone 10 mg/48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: CF</td>
<td>LE: LE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>RE: 20/50</td>
<td>RE: 20/30</td>
<td>Macular scarring RE</td>
<td>Infliximabs 200 mg iv, prednisone 10 mg/day, cyclosporin 100 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: LP+</td>
<td>LE: LP+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>2</td>
<td>RE: 20/400</td>
<td>RE: 20/30</td>
<td>Fibrosis; disc swelling RE</td>
<td>Infliximabs 200 mg iv, cyclosporin 100 mg/day, prednisone 5 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: 20/120</td>
<td>LE: 20/120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>4</td>
<td>RE: 20/200</td>
<td>RE: 20/100</td>
<td>Disc swelling RE+LE</td>
<td>Infliximabs 200 mg iv</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: 20/200</td>
<td>LE: 20/100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>3</td>
<td>RE: 20/40</td>
<td>RE: 20/40</td>
<td>Macular oedema LE</td>
<td>Infliximabs 200 mg iv, MTX 15 mg/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: 20/60</td>
<td>LE: 20/60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>1</td>
<td>RE: 20/120</td>
<td>RE: 20/200</td>
<td>STOP: dermatitis</td>
<td>Infliximabs 200 mg iv, with cyclosporin/MTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE: CF</td>
<td>LE: CF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Effect on inflammation after the first infusion with infliximab

Table 3: Visual acuity after (at least) 2 years follow up in patients with uveitis treated with anti-TNF-α
stopped. This patient deteriorated and is now stable with a VA of 0.1 right eye and counting fingers left eye.

**DISCUSSION**

Anti-TNF-α therapy is promising in the treatment of severe sight threatening uveitis, both in patients with Behcêt's disease and in idiopathic endogenous uveitis. Our series is a selection of patients in whom maximum visual recovery is limited as a result of irreversible ocular damage. Despite the poor recovery of visual acuity—that is, 7/13 patients showed any improvement in vision, whereas 4/13 patients gained two or more lines, a good clinical response was observed regarding inflammation in the majority of these patients. Clinical trials are necessary to determine the optimal therapeutic strategy in patients with uveitis with regard to dosage and duration of treatment. In our series we observed only minor side effects in two patients. In this small case series of refractory uveitis patients, we did not observe any signs or symptoms of lupus erythematosus. However, those patients were initially treated with other immunosuppressive drugs which may suppress auto-antibody formation.

The treatment of posterior uveitis is based on local or systemic immune suppression and the treatment of secondary macular oedema. In most patients, treatment with steroids and immune suppression and the treatment of secondary macular oedema, atrophy, or retinal detachment. Here we show that infliximab administration indeed results in a rapid decrease of the inflammation activity. Anti-TNF-α therapy may be added to the therapeutic regimen in the treatment of patients with sight threatening uveitis including uveitis in Behcêt's disease. However, controlled masked studies are warranted to determine the optimal dosage and duration of the treatment. The effect of co-medication interaction must also be investigated in this new therapy for uveitis.

In conclusion, anti-TNF-α therapy is promising in the treatment of sight threatening uveitis.

**REFERENCES**

Clinical evaluation of the pressure phosphene tonometer in patients with glaucoma

E Rietveld, D A van den Bremer, H J Völker-Dieben

Aim: To evaluate the reliability of the pressure phosphene tonometer in comparison with the Goldmann applanation tonometer.

Methods: 45 consecutive patients with glaucoma (78 eyes) participated in the study. Eyes with previous eye surgery, a documented peripheral visual field defect, a refractive error of more than 5 dioptres, and patients who were unable to understand the procedure were excluded from the study. Intraocular pressure was measured with a pressure phosphene tonometer by one examiner and with a Goldmann applanation tonometer by two other examiners no more than 15 minutes apart. A second series of measurements was performed several weeks later on 34 patients (59 eyes). There was no communication between examiners or between examiner and patient regarding test results.

Results: No statistically significant correlation was found between the applanation tonometry values and those obtained with a pressure phosphene tonometer.

Conclusion: The pressure phosphene tonometer is not suitable for reliably measuring intraocular pressure.

In 1998, Fresco described a method for the self measurement of intraocular pressure and compared its results to the “gold standard” Goldmann applanation tonometer (AT).\textsuperscript{1} The pressure phosphene tonometer (PT) is a device that is able to create a phosphene in a patient’s eye by gradually increasing the pressure on the eyeball via the upper eyelid.

The word phosphene, derived from the Greek words \textit{phos} = light and \textit{plainein} = to show, is used to describe the psychophysical response to a non-physiological stimulus to the eye—that is pressure instead of light. This principle, the perception of light by external pressure on the eyeball, was presumably first described by Alcmaeon of Croton in approximately 600 BC and was later also described by Aristotle, Purkinje, and Von Helmholtz.\textsuperscript{2}

We evaluated the reliability of the PT in the hands of an ophthalmic technician, comparing the results with the values obtained by testing the same patients with the gold standard AT. Self tonometry by the patient was part of the original protocol. However, since the results obtained during the first phase showed no clinical relevance, the protocol was terminated.

Patients and Methods

Patients were recruited for the study between February and June of 2002. Initial selection was based on the examination of the data in the clinical records of the patients. The potential participants were then solicited for voluntary participation during their office visit. Inclusion criteria were an age of 18 years or older, a positive history for glaucoma or a positive family history of glaucoma. Eyes with a history of previous eye surgery, a documented peripheral visual field defect, a refraction of more than 5 dioptres, and patients who were unable to understand the procedure were excluded from the study.

A total of 45 subjects participated in the study. Of these, 34 returned for a second series of measurements. The study group consisted of 24 men (53.3%) and 21 women (46.7%) with a mean age of 62 years (range 33–91 years).

During the first visit, the measurement was taken from the right eye in 43 subjects and in the left eye in 35 subjects. In 13 patients only one eye was measured because of exclusion criteria applicable to the fellow eye. During the second visit, the measurement was taken from the right eye in 33 subjects and from the left eye in 26 subjects. This means that intraocular pressure (IOP) was measured in a total of 137 instances using the pressure PT and compared to a similar number of measurements with the Goldmann AT.

Following explanation of the procedure, written informed consent for participation in the study was obtained, and the ability of the patient to perceive the phosphene was evaluated. In all cases the initial measurements were done with the PT, before any kind of anaesthesia to the eye. The patient was instructed to look down and sideways with almost closed eyelids. Then the PT was brought into position on the nasal side of the upper eyelid and the pressure was gradually increased. If the phosphene could not be perceived, it was usually possible to stimulate the appearance of the phosphene by slowly moving the PT up and down over the medial part of the eyeball. After the ability to recognise the phosphene was confirmed the patient was included in the study.

The first series of measurements was performed in 45 consecutive glaucoma patients (78 eyes). The study measurements were performed as follows. The pressure of the PT against the upper eyelid was gradually increased by the ophthalmic technician until the patient indicated the perception of a phosphene after which the pressure value indicated by the PT was read and recorded. The measurement was performed three times on one or both eyes at intervals of approximately 10–20 seconds. The mean of those three PT values was used in the study. The patients were not informed about the values obtained with the pressure PT since it was a new device under investigation.

Following this procedure one of the ophthalmologists measured the intraocular pressure in both eyes using a calibrated AT. The time between PT and AT measurements varied from 5 minutes to 15 minutes. The ophthalmologist was not aware of the previous results. All measurements were performed in the morning.

A second series of measurements following the same protocol was performed in 34 patients (59 eyes) after a period of 1–8 weeks, this time in the afternoon.

Abbreviations: AT, applanation tonometer; PT, phosphene tonometer

SCIENTIFIC REPORT

The pressure PT was made available by Bausch and Lomb. The action of the PT is based on a calibrated spring attached to a flat circular probe, with a diameter equal to the Goldmann type applanation tonometer. The scale on the PT is divided into 2 mm Hg units and runs from 10 to 40. The PT indicator remains at the position of the highest value measured.

Mean values, standard deviations, and correlation coefficients were calculated using SPSS v9.0 statistical software.

The institutional review board ethics committee approval was not required for this study.

## RESULTS

During the first visit, the mean value measured with AT in the right eye was 19.3 mm Hg with a standard deviation (SD) of 4.9 (n = 43; minimum = 10, maximum = 40). The mean value with PT was 15.9 (SD 2.9) mm Hg (n = 43; minimum = 10, maximum = 27). The mean value measured with AT in the left eye was 18.8 (SD 5.9) mm Hg (n = 35; minimum = 11, maximum = 45). The mean value with PT was 16.7 (SD 4.0) mm Hg (n = 35; minimum = 10, maximum = 30) (table 1). During the second visit, the mean value measured with AT was 21.0 (SD 5.3) mm Hg (n = 33; minimum = 14, maximum = 33). The mean value with PT was 15.0 (SD 2.6) mm Hg (n = 26; minimum = 12, maximum = 25), and the mean value measured with AT was 20.9 (SD 4.9) mm Hg (n = 33; minimum = 14, maximum = 32). The mean value measured with PT was 15.1 (SD 2.0) mm Hg (n = 33; minimum = 12, maximum = 20) (table 2).

If we focus exclusively on the eyes—that is, the 137 times that an eye was measured with a PT and the value was compared with the value measured with the AT, we arrive at the following findings: The mean IOP measured with the AT was 19.9 (SD 5.3) mm Hg (n = 137; minimum = 10, maximum = 45). The mean IOP measured with the PT was 15.7 (SD 3.0) mm Hg (n = 137; minimum = 10, maximum = 30) (table 3).

Figure 1 shows the intraocular pressures measured with AT values on the X axis plotted against the pressures measured with PT on the Y axis. The correlation calculated using Spearman’s rho is −0.141 with a significance of 0.100. When plotting the values of the intraocular pressure measured with the applanation tonometer against the difference between the AT and PT values (fig 2), there is a good linear correlation (correlation coefficient 0.877).
between applanation and pressure phosphene tonometry measurements and the AT values. The results for the separate groups—that is, only right eyes, only left eyes at the first or the second visit consistently showed the same pattern as the overall results.

**DISCUSSION**

The results concerning the main issue, “To what extent are the intraocular pressures measured with the pressure phosphene tonometer comparable with those measured with the Goldmann tonometer?” are much less favourable with regard to the practical applicability and reliability of the pressure phosphene tonometer, than the results presented by Fresco. He observed a mean IOP of 15.5 mm Hg using the applanation tonometer and a mean IOP of 15.2 mm Hg using the pressure phosphene tonometer, a difference of only 0.3 mm Hg.

We observed a considerably larger difference between the measurements provided by the two techniques in our group of patients. The mean IOP measured with the applanation tonometer was 19.9 mm Hg and the mean IOP measured with the pressure phosphene tonometer was 15.7 mm Hg. The difference between those means is considerably larger than can be attributed to interobserver or intraobserver variation. The results of our study do not confirm the correlation coefficient of 0.7 in Fresco’s publication.

Figure 2 clearly demonstrates that the more the applanation tonometry value exceeds 16 mm Hg, the larger also the difference between AT value and PT value becomes. A regression line through these points intersects the line of zero difference at about 16 mm Hg. This suggests that a measurement with the phosphene tonometer yields random values around 16 mm Hg with no relevance to the actual intraocular pressure as measured by applanation tonometry.

In a previous pilot study we found that there was a good correlation between the PT values obtained by a technician and the PT values resulting from self tonometry by the patient. The PT tonometry by the technician however showed a considerably shorter learning curve for the patient.

The pressure point used to stimulate the appearance of a phosphene is the same as the location described by Fresco. The pressure point corresponds to the inferotemporal visual field. That fact is convenient for our purpose, for two reasons. The first reason is that a phosphene can be stimulated most rapidly here. The second reason is that the inferotemporal visual field is usually the final area to become affected by glaucomatous damage.

We conclude that the pressure phosphene tonometer cannot be considered a reliable alternative for Goldmann’s applanation tonometry. We did not succeed in finding a relation between the moment of perception of a phosphene and the intraocular pressure.

**Authors’ affiliations**

E Rietveld, D A van den Bremer, H J Völker-Dieben, Department of Ophthalmology, VU University Medical Center, Amsterdam, Netherlands

Financial support: €250, grant from the Dutch Glaucoma Society.

Competing interests: none declared

Correspondence to: Eelco Rietveld, MD, Department of Ophthalmology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, Netherlands; e.rietveld@vumc.nl

Accepted for publication 1 September 2004

**REFERENCES**


Intraocular pressure variability in patients who reached target intraocular pressure

F K Malerbi, M Hatanaka, R M Vessani, R Susanna Jr

Aim: To assess the intraocular pressure (IOP) variability in patients with primary open angle glaucoma (POAG) under clinical treatment who reached an established target pressure based on isolated office readings.

Methods: Retrospective analysis of 65 eyes from 65 POAG patients under clinical therapy who submitted to modified diurnal tension curve (mDTC) (measurements at every 3 hours between 8 am and 5 pm) followed by a water drinking test (WDT). All subjects had established target IOP ≤ 15 mm Hg at 11 am or 2 pm. IOP variability during mDTC or WDT was evaluated.

Results: mDTC revealed IOP measurements ≥17 mm Hg in 16 of 65 eyes (24.6%). Nine eyes (13.8%) presented values ≥18 mm Hg. The highest IOP detected by mDTC was 20 mm Hg in one patient (1.5%). WDT demonstrated IOP values ≥17 mm Hg in 32 of 65 eyes (49.2%). Twenty-two eyes (33.8%) presented values ≥18 mm Hg after water ingestion. Moreover, IOP levels ≥20 mm Hg were observed in 14 eyes (21.5%).

Conclusion: A great percentage of POAG patients undergoing clinical treatment and with IOP control based on single office measurement present significantly higher IOP measurements when performing mDTC and, especially, the WDT.

Elevated intraocular pressure (IOP) is considered the main risk factor for the development of glaucomatous damage. Glaucoma treatment is based mainly on IOP reduction to a level at which no additional damage is expected to occur. This level, the so-called target IOP, is established on an individual basis and is usually assessed by single office measurements during working hours.

The benefits of IOP lowering have already been demonstrated by previous studies. However, a significant group of patients still develop glaucomatous progression despite IOP values considered within adequate limits. This could be explained by IOP fluctuation during the day or be the result of pressure peaks not detected during office examinations. IOP fluctuation is considered a risk factor for the progression of glaucoma. Drance demonstrated that almost one third of patients with single IOP measurements at office hours had pressure peaks only detected during a 24 hour pressure curve. Thus, monitoring the IOP at times during 24 hours of the day could be considered the best way to assess the IOP profile of glaucomatous patients.

In spite of its importance, a 24 hour diurnal tension curve (DTC) is not always feasible in the routine practice. Alternatively, a modified diurnal tension curve (mDTC) has become a common practice and consists of four to five IOP measurements during office hours (from 8 am to 6 pm). However, this test may miss as much as 70% of IOP peaks as a result of IOP variability and also because up to 70% of the highest IOP levels occur at 6 am in supine position.

Another possible way to assess the IOP is the water drinking test (WDT). Besides being a practical way to estimate the pressure peaks through the 24 hours of the day, the response to this test was also considered a risk factor for the development of glaucomatous visual field progression in open angle glaucoma.

In this study, we assess the IOP variability using the mDTC and the WDT in patients with primary open angle glaucoma (POAG) undergoing clinical treatment who were considered to be well controlled with IOP equal to or under an established target pressure based on isolated office readings.

METHODS

In this retrospective study, we reviewed the charts of 65 POAG patients who submitted to a modified diurnal tension curve (measurements every 3 hours from 8 am to 5 pm) followed by the WDT from the private office of one of the authors (RSJ).

WDT consisted of basal IOP reading followed by ingestion of 1 litre of tap water. IOP was measured afterwards three times at 15 minute intervals. All subjects had an established target IOP level of 15 mm Hg, based on glaucomatous damage level. One eye of each patient was randomly chosen for analysis. All eyes had to present IOP equal to or under 15 mm Hg at a single office reading at 11 am or 2 pm. IOP peaks were evaluated with mDTC and WDT.

RESULTS

In all, 65 eyes of 65 patients were included in this study; 29 (44.6%) patients were male. The mean age of all participants was 65.26 (SD 11.15, range 41–87) years.

Table 1 and figure 1 summarise IOP peaks detected by mDTC and WDT and their frequencies. mDTC revealed IOP measurements ≥17 mm Hg in 16 of 65 eyes (24.6%). Nine eyes (13.8%) presented values ≥18 mm Hg. The highest IOP detected by mDTC was 20 mm Hg in one patient (1.5%). WDT demonstrated IOP values ≥17 mm Hg in 32 of 65 eyes (49.2%). Twenty-two eyes (33.8%) presented values ≥18 mm Hg after water ingestion. Moreover, IOP levels ≥20 mm Hg were observed in 14 eyes (21.5%).

DISCUSSION

Despite IOP reduction obtained with glaucoma treatment, even when pressure levels are apparently well controlled, some patients continue to develop glaucomatous progression. One possible explanation could be the occurrence of IOP peaks not detected during routine examination, as demonstrated by Drance, who found that almost one third of patients with single IOP measurements taken at office

Abbreviations: mDTC, modified diurnal tension curve; POAG, primary open angle glaucoma; WDT, water drinking test
hours had pressure peaks only detected by a 24 hour tension curve. A study from Zeimer et al.23 showed that 29% of patients with progressive visual field damage presented IOP peaks in comparison to 5% of patients with stable visual fields. Also, the occurrence of IOP peaks was related to visual field loss progression in comparison with patients with stable visual fields in a study from Martínez-Belló et al.,17 which also did not demonstrate any significant difference between mean IOP levels of patients who developed progression in comparison to stable ones. These studies support the importance of detecting IOP peaks in glaucoma treatment.

A 24 hour daily tension curve would be a candidate for such task. However, this is a time consuming test associated with structural difficulties and costs as major drawbacks. Thus, other practical methods to detect pressure peaks and to assess fluctuation are needed.

The water drinking test was first described in the 1960s as a diagnostic test for glaucoma. After water ingestion, a 6 mm Hg or 8 mm Hg rise in IOP was considered a positive test for the diagnosis of glaucoma.14 However, this test presented unacceptable false positive and false negative results.18

On the other hand, the WDT presents a good correlation between IOP peaks after water overload and IOP peaks detected during a daily tension curve.14 Also, the importance of this test was demonstrated by Armaly et al.16 In a prospective study of 5000 patients with open angle glaucoma, these authors studied 26 potential risk factors for the development of glaucomatous visual field lesion. From these, only five were considered significant: outflow facility, age, IOP, cup/disc ratio and change in IOP after water ingestion. Moreover, Yoshikawa et al.18 demonstrated that WDT was the main predictive test for glaucomatous progression in a group of patients with normal tension glaucoma.

It has been hypothesised that the WDT could be used as an indirect tool to measure outflow facility. Indeed, Susanna and Medeiros,19 using this test, were able to demonstrate reduced IOP fluctuation in patients controlled with filtering surgery in comparison with those controlled with topical medication.

All these data have changed the concept of the WDT, which is not used as a diagnostic test anymore, but as a useful tool to assess IOP peaks and IOP fluctuation.

In this study the IOP profile of POAG patients undergoing clinical treatment and apparently well controlled, as verified by single office measurements was assessed. This was done with a modified daily tension curve, widely used in general clinical practice, followed by the WDT. Both tests were capable of demonstrating the existence of IOP peaks. However, the frequency of detected peaks was higher when assessed by the WDT, which also demonstrated higher levels of IOP and higher fluctuation.

One explanation for this difference could be the fact that the modified daily tension curve does not measure the IOP during the times when it is expected to be higher (for example, 6 am) which, in turn, could be a result of the supine position of the patient at the time of measurement. Indeed, Hirooka and Shiraga20 found a significant difference between IOP levels measured in the sitting and supine positions, the greater differences being in eyes with worse visual field damage. It is worth noting that their results suggested that more glaucomatous damage could happen during sleep in the supine position.

On the other hand, assuming that the WDT has a good correlation with the IOP peaks detected during a 24 hour daily tension curve, it is reasonable to accept that these high IOP levels are actually occurring through the day, presenting a considerable risk for the progression of the disease and which were revealed by this promising test. Moreover, this is an easy test to perform, involving the natural and physiological act of drinking water.

In summary, our data demonstrate the importance of a careful assessment of IOP profile in glaucomatous patients, even when clinical treatment seems to be adequate. The modified daily tension curve can demonstrate IOP peaks, although with lower frequency and lower amplitude in comparison with the water drinking test. This study also

### Table 1 Frequency of IOP peaks detected by mDTC and WDT

<table>
<thead>
<tr>
<th>Maximum IOP detected (mm Hg)</th>
<th>Verified by mDTC</th>
<th>Verified by WDT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>%</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>13</td>
<td>6</td>
<td>9.2</td>
</tr>
<tr>
<td>14</td>
<td>8</td>
<td>12.3</td>
</tr>
<tr>
<td>15</td>
<td>20</td>
<td>30.8</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>15.4</td>
</tr>
<tr>
<td>17</td>
<td>7</td>
<td>10.8</td>
</tr>
<tr>
<td>18</td>
<td>7</td>
<td>10.8</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>22</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>23</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Figure 1 Frequency of IOP peaks detected by modified diurnal tension curve (mDTC) and water drinking test (WDT) (cumulative frequencies).
emphasises the value that the water drinking test may have as a complementary test in clinical practice.

Authors’ affiliations
F K Maleberi, M Hatanaka, R M Vessani, R Susanna Jr, Glaucoma Department, University of Sao Paulo School of Medicine, Sao Paulo, Brazil

Correspondence to: Fernando Korn Maleberi, Glaucoma Department, University of Sao Paulo School of Medicine, Sao Paulo, Brazil, Rua Capote Valente 171 Ap 122, Sao Paulo, SP, Brazil, 05409-000; marcelohatanaka@uol.com.br

Accepted for publication 23 October 2004

REFERENCES

ECHO

Long sight reduces learning in young schoolchildren

Children are failing educationally because long sight is not seen as a problem, say doctors in South Wales who have studied more than a thousand schoolchildren.

Scores for national tests—proficiency in reading and writing English and progress in the national curriculum in English, mathematics, and science—were significantly lower for the children who had been referred to an optometrist and were the most long sighted (>+3D for both eyes or >1.25 for best eye) than for those who were less affected (<=+3D) and for those who had not been referred. Thirteen per cent of the total cohort had been referred to an optometrist after failing a test for long sight, and half of them needed glasses or a referral to an educational psychologist, or both. Many of those referred to the psychologist scored poorly in the tests.

The local community paediatric service screened almost 1300 children aged 8 years with a standard vision screening protocol changed to include a fogging test for long sight. Children failing this test or others were referred to an optometrist for treatment and possible further referral to an educational psychologist. Educational test results were obtained for consenting children.

This study tested the extent to which long sight is undiagnosed in young schoolchildren and confirmed its detrimental effect on learning. There is widespread dissent on vision screening standards and methods; screening for long sight is not performed in most schools; and the effectiveness of present preschool screening services has been questioned.

A novel index for predicting intraocular pressure reduction following cataract surgery

S A Issa, J Pacheco, U Mahmood, J Nolan, S Beatty

Aim: The results of a study designed to investigate the predictive value of preoperative anterior chamber depth (ACD) and intraocular pressure (IOP) are reported. The relation between these factors and their effect on the reduction in IOP following phacoemulsification cataract surgery was also studied.

Methods: The ACD and IOP were prospectively measured in 103 non-glaucomatous eyes of 103 patients who underwent uneventful phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation. Other data which were recorded included best corrected visual acuity, axial length, lens thickness, and severity of lens opacity.

Results: The ACD increased by a mean (SD) of 1.10 (0.44) mm (p < 0.00001) and this increase was significantly and inversely related to preoperative ACD (r² = 68%; p < 0.01). IOP dropped by a mean of 2.55 (1.78) mm Hg following cataract surgery (p < 0.0001), and this reduction was significantly and positively related to preoperative IOP (r² = 56%; p < 0.01), and significantly and inversely related to preoperative ACD (r² = 21%; p < 0.01). A novel ratio, the pressure to depth (PD) ratio (preoperative IOP/preoperative ACD), was found to be significantly and positively related to the surgically induced reduction in IOP (r² = 73%; p < 0.01), and IOP was reduced by > 4 mm Hg in all patients with a PD ratio > 7.

Conclusion: The reduction in IOP following cataract surgery was found to be positively related to preoperative IOP, and inversely related to preoperative ACD. Furthermore, these results indicate that a novel index, the PD ratio, is strongly predictive for IOP reduction following cataract extraction, and may prove useful in surgical decision making.

RESULTS

We studied 103 eyes (57 left and 46 right eyes) of 103 volunteers. Mean age (SD) was 76.07 (9.33) years (table 1). Data were analysed by SPSS software package (version 11) and differences between preoperative and postoperative values were assessed by the paired Student two tailed t test. Categorical data were analysed using the χ² test, and correlations between continuous data were assessed using the Pearson correlation coefficient. Multiple linear regression was performed in order to investigate the relation between IOP drop and several variables. A p value of less than 0.05 was considered statistically significant.

Abbreviations: ACD, anterior chamber depth; ACG, angle closure glaucoma; AXL, axial length; BCVA, best corrected visual acuity; IOP, intraocular pressure; PCIOL, posterior chamber intraocular lens; PD ratio, pressure to depth ratio
and 43.7% were male and 56.3% were female. BCVA was found to improve significantly from 0.6 (0.53) to 0.2 (0.2) (p<0.00001).

Mean preoperative and postoperative ACD were 2.97 (0.44) mm and 4.07 (0.34) mm, respectively, and this represented a mean increase of 1.10 (0.44) mm (p=0.00001) (fig 1). There was a statistically demonstrable inverse relation between preoperative ACD and the extent of ACD increase (r = −0.8215, r² = 68%; p<0.01).

Mean lens thickness was 4.30 (0.59) mm and was positively related to the increase in ACD (r = 0.306; p = 0.002), but was not significantly related to changes in IOP (p = 0.579). It was also noted that lens thickness was inversely related to preoperative ACD (r = −0.332; p = 0.001).

The mean grade of lens opacification was 4.2 (1.1) for nuclear opalescence; 4.2 (1.1) for nuclear colour; 2.4 (1.5) for cortical lens opacity; and 1.8 (1.9) for posterior subcapsular opacities, and none of these were significantly related to changes in IOP (range of p: 0.069–0.916) or ACD (range of p: 0.073–0.217).

Of note, no statistically significant difference in terms of changes in ACD or IOP could be attributed to PCiol type (ACD: p = 0.572; IOP: p = 0.665) and there was no statistically significant difference between preoperative and postoperative AXL (p = 0.1444).

Mean preoperative and postoperative IOP were 15.23 (2.47) mm Hg and 12.68 (1.65) mm Hg, respectively, and this represented a mean drop of 2.55 (1.78) mm Hg (p=0.00001). The extent of IOP reduction postoperatively was inversely related to preoperative IOP (r = −0.745; r² = 56%; p<0.01) (fig 2). Furthermore, it was noted that IOP reduction was inversely related to preoperative ACD (r = −0.455; r² = 21%; p<0.01) (fig 3). Other variables including age, sex, lens thickness and preoperative AXL were not significantly related to IOP reduction (multivariate analysis) (range of p values: 0.174–0.869).

We investigated the predictive value of a novel ratio (preoperative IOP/preoperative ACD), and named this the pressure to depth ratio, or PD ratio. The PD ratio was positively related to the extent of IOP reduction (r = 0.852; r² = 73%; p<0.01) (fig 4). Twenty nine eyes (28%) had a PD ratio >6.0, and they exhibited a mean reduction in IOP of 4.90 (1.34) mm Hg, and this reduction was significantly greater than for eyes with a PD ratio<6.0 who had a mean IOP reduction of 1.64 (0.84) mm Hg (p<0.001). Furthermore, 96% of eyes with a PD ratio >6.0 exhibited an IOP drop of ≥2 mm Hg, compared with only 38% of those with a PD ratio<6.0.

Figure 1 The relation between preoperative and postoperative ACD after cataract surgery. The solid line plotted is the line of equivalence.

Figure 2 The relation between preoperative IOP and IOP reduction after cataract surgery. Note that IOP drop is plotted as a positive value. Random noise of not more than plus or minus 0.1 was superimposed onto both x and y values to ensure that a maximum number of data points were visually represented. ACD, anterior chamber depth; IOP, intraocular pressure.

Figure 3 The relation between preoperative ACD and IOP reduction following cataract surgery. Note that IOP drop is plotted as a positive value. Random noise of not more than plus or minus 0.1 was superimposed onto IOP drop values to ensure that a maximum number of data points were visually represented. ACD, anterior chamber depth; IOP, intraocular pressure.
Predicting IOP reduction following cataract surgery

Figure 4 The relation between PD ratio and IOP reduction following cataract surgery. Note that IOP drop is plotted as a positive value. Random noise of not more than plus or minus 0.1 was superimposed onto IOP drop values to ensure that a maximum number of data points were visually represented. IOP, intraocular pressure; PD ratio, intraocular pressure to anterior chamber depth ratio.

The major limitation of our study resides in its short follow up period. However, previous investigators have shown that the IOP lowering effect of phacoemulsification persists for at least 12 months.21 Also, we did not measure corneal thickness which could influence IOP measurements, as increased corneal thickness has been associated with falsely high IOP readings in previous studies.27-29

In conclusion, we describe a ratio that incorporates preoperative ocular parameters, which can be easily measured in a clinical setting, and appears to be strongly predictive for IOP reduction following cataract surgery in non-glaucomatous eyes. Eyes with a higher PD ratio exhibited a greater reduction in IOP. Further study, with longer follow up, is needed to investigate the potential role of the PD ratio in non-glaucomatous and glaucomatous eyes if its value in surgical decision making is to be confirmed or refuted.

DISCUSSION

We have shown that ACD increased significantly by a mean of 1.10 mm 8 weeks postoperatively, which is comparable to reports of Hayashi et al.13 They also found that, after surgery, the ACD in eyes with angle closure glaucoma (ACG) became almost identical to those in the non-glaucomatous eyes, indicating that cataract extraction may negate the anatomical predisposition to ACG.13 Indeed, Gunning and Greve advocated cataract extraction for ACG as they found that it resulted in IOP reduction to the same extent as did filtering surgery, with fewer complications.12

Several studies have demonstrated that cataract extraction and IOL implantation lowers IOP to some extent in eyes with primary open angle glaucoma (POAG)14-20 and non-glaucomatous eyes,21-23 and that this IOP reduction lasts for at least 12 months after phacoemulsification surgery in non-glaucomatous eyes.13,22 However, previous workers have not investigated preoperative parameters which may be of predictive value for IOP reduction following cataract surgery.

We have demonstrated a significant IOP reduction, by a mean of 2.55 mmHg, 8-9 weeks after cataract surgery in non-glaucomatous eyes, which is comparable to a study by Tong et al.21 This reduction in IOP was more marked in patients with a higher preoperative IOP, and we also showed that this reduction was inversely related to preoperative ACD. The observation that lens thickness was positively and negatively related to increases in ACD and preoperative ACD, respectively, suggests that any relation that might exist between lens thickness and IOP reduction following cataract surgery is likely to be mediated through its relation with ACD. In our study comprising 103 eyes, no significant relation between lens thickness and surgically induced IOP reduction was observed.

A novel ratio, incorporating preoperative ACD and IOP, was found to be more strongly predictive for IOP reduction following cataract surgery ($r^2 = 73\%$) than either of these parameters in isolation ($r^2 = 21\%$ for ACD and $56\%$ for IOP). Thus, the PD ratio may be a useful tool in the management of non-glaucomatous eyes where a high IOP reduction is desirable and where cataract exists.

Tong et al have shown that IOP reduction was statistically similar for non-glaucomatous and glaucomatous eyes 6 months after phacoemulsification and PCIOIL implantation.21 Others have found that the reduction in IOP after cataract extraction can allow for reduced use of postoperative antiglaucoma medication in POAG patients.25 Should the predictive value of the PD ratio be confirmed in further study on eyes with POAG, it may be reasonable to incorporate its use into the surgical decision making process in an attempt to avoid the greater risk of complications inherent in glaucoma filtration surgery when compared with cataract surgery.24,25

Mechanisms that have been hypothesised to explain the reduction in IOP following cataract surgery include: improvement of aqueous outflow facility by widening the drainage angle13,26; and/or an effect on the ciliary body (by capsular bag contraction) which results in reduced aqueous production.12 Although the mechanism of IOP reduction following cataract surgery remains uncertain, our results indicate that it is a function of both preoperative ACD and IOP.

REFERENCES


Effects of the combination of bimatoprost and latanoprost on intraocular pressure in primary open angle glaucoma: a randomised clinical trial

L M Doi, L A S Melo Jr, J A Prata Jr

Aims: To evaluate the effect of the combination of bimatoprost and latanoprost on intraocular pressure (IOP) in primary open angle glaucoma (POAG).

Methods: An open label randomised clinical trial was conducted, which included 18 glaucomatous patients (36 eyes). In the first 4 weeks, latanoprost 0.005% was prescribed for both eyes of the patients and any other antiglaucoma medication was discontinued. In the next 4 weeks (phase 1), bimatoprost 0.03% was combined with latanoprost in one randomly assigned eye (case eye) of each patient. In the next 4 weeks (phase 2), bimatoprost was discontinued in the case eyes, while bimatoprost was substituted for latanoprost in the fellow eye (control eye). The IOP was measured at the end of the first 4 weeks (baseline measurement) and weekly during phases 1 and 2.

Results: In the case eyes, the mean IOP increased along the first phase (1.8 mm Hg; p = 0.006) when compared to baseline measurements. The IOP returned to previous values after discontinuation of bimatoprost in phase 2. In the control eyes, the mean IOP did not change throughout the study.

Conclusion: The combination of bimatoprost and latanoprost in POAG increases the IOP and should not be considered as a therapeutic option.

The combination of bimatoprost and latanoprost could produce an additive intraocular pressure (IOP) lowering effect, considering the mechanisms of action of these medications. Most of their effect is on uveoscleral outflow, where they act, probably, on different receptors. However, one medication could also interfere with the IOP lowering effect of the other, leading to an increase in IOP, as it was observed in a case series of three glaucomatous patients.

We are unaware of a published comparative clinical trial evaluating the combination of these medications and could find no reference to it in a Medline based search. Therefore, this clinical trial was conducted to evaluate the effect of the combination of bimatoprost and latanoprost on IOP in primary open angle glaucoma (POAG).

Patients and Methods

A 12 week open label randomised clinical trial was performed. The protocol was approved by the ethics committee of the Federal University of São Paulo and was in compliance with the Declaration of Helsinki. All patients gave their informed consent.

Study population

This study enrolled patients with POAG who were treated at the Federal University of São Paulo. Slit lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, funduscopy using a 78 dioptre lens, and automated static perimetry (Humphrey Sita 24–2, Carl Zeiss Meditec, Dublin, CA, USA) examinations were performed to select the patients.

Patients were eligible for the study if they met all of the following criteria in both eyes: (1) alterations of the optic nerve head (vertical cup to disc ratio of more than 0.5, notching, splinter haemorrhage, acquired pit) and visual field defects (defects of three or more contiguous points with a probability of less than 5% in a non-edge localisation at the pattern deviation plot) suggestive of glaucoma; (2) gonioscopy demonstrating a 360° normal appearing open angle; (3) IOP >21 mm Hg; and (4) no ocular or systemic findings that could justify an ocular hypertension.

Exclusion criteria included the presence of advanced glaucoma, IOP >30 mm Hg despite the use of antiglaucoma medications, previous intraocular surgery, patients younger than 18 years, pregnancy or lactation, inability to make return visits, and use of corticosteroids. The glaucoma was considered advanced if the patients presented an optic nerve head with vertical cup to disc ratio of more than 0.8, or visual field defects threatening the central fixation or mean deviation (MD) <-12 dB.

Intervention procedures

The patients were instructed to instil once daily latanoprost 0.005% (Xalatan, Pfizer) in both eyes in the evening (between 7 pm and 9 pm) for 4 weeks. Any other antiglaucoma medication was discontinued. At the end of this period, the IOP was measured and recorded as the baseline measurement (fig 1). Patients with baseline IOP measurements higher than 30 mm Hg in either eye were excluded from the study, others were entered into phase 1.

In phase 1, once daily bimatoprost 0.03% (Lumigan, Allergan), instilled in the morning (between 7 am and 9 am), was added to the prescription in one of the patient’s eyes (case eyes). The patient’s eye treated with a combination of bimatoprost and latanoprost was randomly assigned using a sealed envelope technique. During this 4 week phase, the patients had their IOP measured in both case and control eyes weekly. The patients would be excluded from the study if the IOP increased more than 12 mm Hg from the baseline measurement or any severe ocular complication was detected.

In phase 2, bimatoprost was discontinued from the case eyes. In the control eyes, once daily bimatoprost 0.03% in the evening (between 7 pm and 9 pm) was substituted for latanoprost. During this 4 week phase, the patients also had their IOP measured weekly.

Abbreviations: IOP, intraocular pressure; MD, mean deviation; POAG, primary open angle glaucoma
Throughout the study, IOP measurements were performed between 10 am and 12 pm using a Goldmann applanation tonometer. The examiner was masked for the groups before measuring the IOP. In all visits, the patients were asked about the medication regimen to ensure that the prescription had been followed correctly.

Statistical analysis

Repeated measures analysis of variance (ANOVA) was performed for the analysis of IOP data. In cases of missing IOP values, the mean IOP value of the two adjacent visits was used. To determine whether the IOP changes were different between the two groups throughout phase 1, an analysis of the interaction between visits and groups was performed. The Dunnett test was used for post hoc multiple comparisons in the case group and the baseline IOP measurement was used as the reference value. With 18 eyes for each group and five visits (baseline—week 4), this design achieved 90% power to detect an effect standard deviation of 0.45 mm Hg (an effect size of 1.14) within each group. The significance level was set at 0.05.

RESULTS

All of the 18 patients included completed the study. Five patients missed visits (two patients at week 2 and three patients at week 3). Five patients were male and 13 were female, and the mean (SD) age was 63.5 (9.7) years. Fourteen patients were white and four were black. Eleven right and seven left eyes were randomised to receive the addition of bimatoprost and latanoprost. None of the participants was using latanoprost and two patients (four eyes) were using bimatoprost at the time of enrolment.

The IOP of case and control eyes from baseline to week 8 are summarised in Table 1. The interaction between group and visits (from baseline to week 4) was statistically significant (p = 0.009; fig 2). In the case eyes, the IOP changed from baseline to week 8 (p = 0.005). The IOP increased from baseline to week 4 (p = 0.013). The data from weeks 2, 3, and 4 showed statistically significant higher IOP measurements than baseline (table 1). The mean (95% confidence interval) increases in IOP from baseline to weeks 2, 3, and 4 were 1.7 mm Hg (0.2 to 3.1), 1.6 mm Hg (0.2 to 3.0) and 1.8 mm Hg (0.4 to 3.3), respectively. After phase 1, the IOP decreased to values close to the baseline measurements (fig 2). Conversely, in the control eyes, the mean IOP did not change either from baseline to week 4 (p = 0.669), or from week 4 to week 8 (p = 0.459). Although mild conjunctival hyperaemia was

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Intraocular pressure (IOP) throughout the study according to group and visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>IOP (mm Hg)</strong></td>
</tr>
<tr>
<td><strong>Visits</strong></td>
<td><strong>Mean (SD)</strong></td>
</tr>
<tr>
<td>Baseline</td>
<td>15.3 (3.5)</td>
</tr>
<tr>
<td>Week 1</td>
<td>16.3 (2.9)</td>
</tr>
<tr>
<td>Week 2</td>
<td>17.0 (3.0)</td>
</tr>
<tr>
<td>Week 3</td>
<td>16.7 (3.1)</td>
</tr>
<tr>
<td>Week 4</td>
<td>17.2 (3.3)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>15.8 (3.2)</td>
</tr>
<tr>
<td>Week 5</td>
<td>15.7 (2.8)</td>
</tr>
<tr>
<td>Week 6</td>
<td>15.9 (3.3)</td>
</tr>
<tr>
<td>Week 7</td>
<td>15.8 (3.5)</td>
</tr>
</tbody>
</table>

*Dunnett test, baseline measurement used as reference.
noted in a few eyes, no patients discontinued the study because of any adverse effects of the medications.

DISCUSSION
In this study, IOP increased in eyes treated with the combination of latanoprost and bimatoprost. Herndon et al described increases in IOP of 23, 15, and 23 mm Hg in a case series of three patients using latanoprost in combination with bimatoprost; 11 mm Hg was the maximum IOP increase in our study. Differences in the type and stage of glaucoma could be related to this discrepancy. In the paper by Herndon et al, one patient had pigmentary glaucoma and another had angle closure glaucoma. In our series, all patients had POAG. Since we did not include patients with advanced glaucoma, we could not determine whether IOP changes in advanced glaucoma are different from early or moderate stages of this disease.

The reason for the IOP increase with the adjunctive use of both medications could not be clarified in our study. Although bimatoprost and latanoprost could act by different receptors, they share similar characteristics regarding alterations in IOP according to doses and regimens of administration. Latanoprost and bimatoprost produce a greater IOP reduction with single than multiple daily doses. Proposed hypotheses for this effect are reduction of the uveoscleral outflow, increase in episcleral venous pressure of short duration, development of subsensitivity at the FP receptor or intracellular pathways, compromise in the classic pathway, and it was also speculated that a twice daily regimen presents a dose beyond the dose-response curve, resulting in a consequently lower effect.

The fact that the free acid of bimatoprost is a potent FP receptor agonist and enzymes in mammalian ocular tissues may hydrolyse bimatoprost to its free acid could account for the increase in IOP observed in the adjunctive use of bimatoprost and latanoprost. These facts argue favourably that a common receptor for both drugs may be involved. Thus, the concurrent use of both drugs could increase the IOP observed with the adjunctive use of bimatoprost and latanoprost. These facts argue favourably that a common receptor for both drugs may be involved. These facts argue favourably that a common receptor for both drugs may be involved.

When the medications were administered together, latanoprost was used in the evening and bimatoprost in the morning. Different results might be seen if the two medications were administered a few minutes apart in the evening. Lindén and Alm observed that the administration of three drops of latanoprost with a 5 minute interval did not alter significantly the IOP lowering effect of this medication. Conversely, twice daily (12 hour interval) doses decreased the effect of the latanoprost in that study.

In the control eyes, the change of the drugs used in phase 2 could lead to an IOP increase, as the washout period for latanoprost can extend up to 8 weeks. However, this increase in IOP was not observed. Probably, the residual effect of the latanoprost was not sufficient to interfere with the mechanism of bimatoprost action.

In conclusion, the combination of bimatoprost and latanoprost should not be considered as a therapeutic option in POAG because of the paradoxical increase in IOP.

Authors’ affiliations
L M Doi, L A S Melo Jr, J A Prata Jr, Department of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil
J A Prata Jr, Faculdade de Medicina do Triângulo Mineiro, Uberaba, Brazil

Competing interests: The authors have no financial interests in any drug mentioned in this study.

Ethics approval: The protocol was approved by the ethics committee of the Federal University of São Paulo.

Correspondence to: Luiz Alberto S Melo Jr, R Leandro Dupret 488/161, São Paulo, Brazil 04025-012; luizalberto@oftalmo.epm.br

Accepted for publication 1 October 2004

REFERENCES
4 Toris CB, Camras CB, Yablonki ME. Effects of PhX41, a new prostaglan din F2a analog, on aqueous humor dynamics in human eyes. Ophthalmology 1993;100:1297–304.
18 Stewart WC, Holmes KT, Johnson MA. Washout periods for brimonidine 0.2% and latanoprost 0.005%. Am J Ophthalmol 2001;131:798–9.
Background: Age related macular degeneration (AMD) causing visual impairment is common in older people. Previous studies have identified smoking as a risk factor for AMD. However, there is limited information for the older population in Britain.

Methods: Population based cross sectional analytical study based in 49 practices selected to be representative of the population of Britain. Cases were people aged 75 years and above who were visually impaired (binocular acuity <6/18) as a result of AMD. Controls were people with normal vision (6/6 or better). Smoking history was ascertained using an interviewer administered questionnaire.

Results: After controlling for potentially confounding factors, current smokers were twice as likely to have AMD compared to non-smokers (odds ratio 2.15, 95% CI 1.42 to 3.26). Ex-smokers were at intermediate risk (odds ratio 1.13, 0.86 to 1.47). People who stopped smoking more than 20 years previously were not at increased risk of AMD causing visual loss. Approximately 28 000 cases of AMD in older people in the United Kingdom may be attributable to smoking.

Conclusion: This is the largest study of the association of smoking and AMD in the British population. Smoking is associated with a twofold increased risk of developing AMD. An increased risk of AMD, which is the most commonly occurring cause of blindness in the United Kingdom, is yet another reason for people to stop smoking and governments to develop public health campaigns against this hazard.

Visual impairment is common in older people in Britain. Its prevalence increases progressively with increasing age. Age related macular degeneration (AMD) is the most important cause of visual impairment. Currently there are estimated to be approximately 200 000 people aged 75 years and above visually impaired due to AMD in the United Kingdom. There is no treatment that can restore visual loss in people with AMD. In order to develop preventive strategies we need to understand why some people develop AMD and others do not.

Previous studies have identified smoking as a risk factor for AMD. However, these studies have not included many people aged 75 years and above, which is the population group that bears the burden of AMD in the United Kingdom. In addition, to our knowledge there have been no published studies in the British population that have examined this risk factor specifically.

The population based MRC trial of the assessment and management of older people in the community is a large cluster randomised trial taking place in 106 general practices from the MRC General Practice Research Framework. The practices in the study were selected to be representative of the mortality (SMR) and Jarman scores of general practices in Britain (England, Wales, and Scotland). The aim of the trial was to compare the cost effectiveness of different methods of assessment and management of older people in the context of the 1990 contract of service which required general practitioners to offer an annual health check to patients aged 75 years and over. The study compared two different types of multi-dimensional assessment (targeted versus universal) and two different management models (primary care team versus multidisciplinary geriatric evaluation team). Randomisation was at the practice level and stratified by SMR and Jarman score. All patients aged 75 years or over on the general practitioner list were invited to participate in the trial, unless they were in long stay hospital or nursing homes, or were terminally ill.

People in the 53 practices allocated to the “universal” arm of the trial were given a visual acuity test as part of a detailed health assessment by the practice nurse. Visual acuity was measured at 3 metres with a Glasgow acuity chart which measures the minimal angle of resolution on a logarithmic scale (logMAR). Binocular visual acuity was measured first, followed by vision in the right and left eyes. All vision measurements were conducted with usual spectacle correction. People with visual acuity of 0.5 or more in either eye (equivalent to less than 6/18 Snellen acuity) were retested with a pinhole occluder. If vision did not improve to less than 0.5, and the cause of visual loss had not previously been investigated, the person was referred to an ophthalmologist. If vision improved to less than 0.5, the patient was advised to see an optometrist. Visual impairment was defined as presenting binocular acuity of less than 6/18 (logMAR score 0.5 or more). In 49 practices, the cause of visual impairment was assessed by medical record review. The trial and additional data collection on causes of visual loss were approved by the relevant local research ethics committees.

People with AMD causing visual impairment were considered as “cases” and compared to a “control” group. There were two different options for selection of the control group. Firstly, to compare people visually impaired due to AMD with the rest of the MRC trial study population. This control group would include people visually impaired as a result of other...
causes and people not visually impaired. The second option considered was to compare people visually impaired due to AMD with people with good vision (that is, visual acuity of 6/6 or better).

The signs and symptoms of AMD form a continuous spectrum. Dichotomising the disease, as in many other conditions, is essentially arbitrary. In this study, relatively severe AMD cases were selected because a cut-off point of visual acuity worse than 6/18 was used to identify them. It is likely that a small proportion of people with vision worse than 6/6 and better than, or equal to, 6/18 will have AMD and a larger proportion will have early related maculopathy (ARM)—that is, drusen and pigmentary changes putting them at increased risk of developing AMD. For this reason, in order to minimise the number of controls who have AMD or ARM, a control group of people with good vision—that is, binocular visual acuity of 6/6 or better, was selected.

Smoking history was ascertained using an interviewer administered questionnaire. The questions used came from the Whitehall study. Participants were asked whether they smoked currently. For people who responded no, they were asked whether they had ever smoked cigarettes. Age smoking started and stopped was also elicited and the number of cigarettes (ounces (g) tobacco) smoked a day. One ounce (28 g) of tobacco was assumed to correspond to 30 cigarettes.

The following variables were created:

- Smoking status 1 = never smoked 2 = ex-smoker 3 = current smoker.
- Pack years were calculated from the number of years participants had smoked, multiplied by the usual daily cigarette equivalent intake, and divided by 20. This gives a measure of the lifetime exposure dose received.
- The number of years since stopping smoking was calculated from the current age minus the age stopped smoking. People who were still smoking had a value of 0; people who had never smoked were excluded from this variable.

The following confounding factors were considered because they have been reported in other studies as putative risk factors for AMD: socioeconomic status, alcohol consumption, cardiovascular disease and its risk factors. Data were not available on antioxidant micronutrient intake, exposure to light (visible or ultraviolet), and family history of AMD.

All regression analyses took account of the extra variation introduced by the cluster design of the study using the “svy” commands in Stata version 8.0 (Stata Corporation, TX, USA). “Svy” commands calculate robust standard errors using the “linearisation” variance estimator (based on a first order Taylor series linear approximation).

RESULTS

Controls were younger and less likely to be women (table 1); 9.0% of the study population were current smokers. Smoking decreased with increasing age (p<0.001) and was higher in men (11.2%) than women (7.3%) (p<0.001). Table 2 shows the association between current smoking and risk of AMD causing visual impairment by age.

After controlling for potentially confounding factors, current smokers were twice as likely to be a case compared to non-smokers (odds ratio 2.15, 95% CI 1.42 to 3.26) (table 3). There was little or no association for ex-smokers (odds ratio 1.13, 0.86 to 1.47). There was an increased chance of AMD causing visual loss with increasing pack years of smoking, however, this increase was not seen consistently after controlling for confounding factors.

There was an increased association of AMD with decreasing years since stopping smoking (test for linear trend p<0.001). People who stopped smoking more than 20 years previously did not have increased odds of AMD causing visual loss. There was a moderately increased odds ratio for AMD for people who stopped smoking 10–20 years ago. The adjusted odds ratio comparing people who had stopped smoking 10–<20 years ago with those who had stopped smoking 20 years ago or more or who had never smoked was 1.46 (95% CI 1.03 to 2.07). Comparing people who were current smokers, or who had stopped smoking less than 10 years ago, with people who had stopped smoking 20 years ago or more, or who had never smoked, gave an adjusted odds ratio of 2.29 (95% CI 1.69 to 3.10).

Based on current estimates of the number of people with AMD causing visual loss in the United Kingdom, this equates to approximately 28 000 people (95% CI 17 000 to

<table>
<thead>
<tr>
<th>Age group</th>
<th>Odds ratio*</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>75–79</td>
<td>2.89</td>
<td>1.40 to 5.94</td>
<td>0.003</td>
</tr>
<tr>
<td>80–84</td>
<td>1.85</td>
<td>1.09 to 3.15</td>
<td>0.022</td>
</tr>
<tr>
<td>85–89</td>
<td>1.38</td>
<td>0.69 to 2.78</td>
<td>0.361</td>
</tr>
<tr>
<td>90+</td>
<td>0.93</td>
<td>0.25 to 3.44</td>
<td>0.915</td>
</tr>
</tbody>
</table>

*Mantel-Haenszel estimate of the odds ratio controlling for the effects of age = 1.78 (95% confidence intervals 1.26 to 2.52) p=0.001.

*Odds of being a case if current smoker divided by odds of being a case if a non-smoker.

Table 1 "Cases" are people with AMD causing visual impairment. "Controls" are people with 6/6 vision or better (binocular acuity). Data from the 49 practices taking part in vision add-on study to the MRC Trial of the Assessment and Management of Older People in the Community.
DISCUSSION
This is the largest study of the association of smoking and AMD in the British population and one of the largest reported to date internationally. The results fit in remarkably well with results seen in studies from other countries with different designs, ages studied, and methods of ascertainment of AMD.6–10,20 Smoking is associated with a twofold increased risk of developing AMD. The benefit for stopping smoking is seen after 10 years with reductions in risk although risks do not return to that of never smokers till 20 years after stopping. The result for smoking is also consistent with the known pro-oxidant damage due to tobacco—for example, through DNA damage.21,22

We estimate that approximately 28,000 cases of AMD in older people in the United Kingdom may be attributable to smoking. This is lower than estimates published in a recent editorial (34,000).25 Our study provided a lower estimate of risk (twofold instead of threefold) and we used more conservative estimates of the population burden of AMD. In addition, our age range was more restricted (75 years and older rather than 70 years plus).

In contrast with other studies, we did not find a consistent dose-response relation with pack years of smoking. This may be the result of the difficulty of remembering and assessing smoking exposure over a lifetime in this elderly population.

The current study was limited by not having information on antioxidant intake. One alternative explanation is that smokers eat less fruit and vegetables and thereby increase their risk of AMD. However, other studies have been able to adjust for plasma levels of antioxidant micronutrients and have reported similar size effects for smoking.24

An increased risk of AMD, which is the most commonly occurring cause of blindness in the United Kingdom, is yet another reason for people to stop smoking and governments to develop public health campaigns against this hazard.

Authors’ affiliations
J R Evans, International Centre for Eye Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
A E Fletcher, Non Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
R P L Wormald, Moorfields Eye Hospital and International Centre for Eye Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Source of funding: The MRC Trial of the Assessment and Management of Older People in the Community was funded by the United Kingdom Medical Research Council, the Department of Health and the Scottish Office. Collection of data on causes of visual impairment was funded by the Gift of Thomas Pocklington. Researchers were independent of the funding body.

Competing interests: none declared

Correspondence to: Jennifer R Evans, International Centre for Eye Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK; Jennifer.evans@lshtm.ac.uk

Accepted for publication 3 September 2004

REFERENCES
9 Evans JR, Fletcher AE, Wormald RPL. Causes of visual impairment in people aged 75 years and above in Britain: an add-on study to the MRC Trial of Assessment and Management of Older People in the Community. Br J Ophthalmol 2002;86:345–70.
10 Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular


Get published within days of acceptance with BJO

We are delighted to announce that the British Journal of Ophthalmology launched a “publish ahead of print” programme in March 2005. Selected papers are fast tracked and published online months before they appear in the print journal.

Papers of more significance to the international ophthalmology community are published within days of acceptance. The first published article is the raw accepted manuscript; edited and typeset versions are also published as soon as they are available.

In addition to being available on BJO Online, the publish ahead of print articles are searchable through PubMed/Medline — establishing primacy for your work. They are linked from the BJO Online home page.

The BJO’s publish ahead of print programme is unique among the major ophthalmology journals — to take advantage of this service submit your papers to the British Journal of Ophthalmology using our online submission and review system Bench>Press (http://submit-bjo.bmjournals.com). For further information contact the editorial office (US office choyt@itsa.ucf.edu or the UK office anne.williams@bristol.ac.uk).
SCIENTIFIC REPORT

An interinstitutional comparative study and validation of computer aided drusen quantification

V Sivagnanavel, R T Smith, G B Lau, J Chan, C Donaldson, N V Chong

METHODS

Colour fundus images (Topcon TRC 50IX retinal camera) from 10 patients were selected at random from the digital database at Kings College Hospital (KCH) with stage 2 or 3 age related maculopathy (ARM) (as defined by the international grading system). Extensive hyperpigmentary or hypopigmentary abnormalities were excluded. Images were analysed by the methods described previously. Briefly, the images used had minimum resolutions of 2700 pixels/inch. The images were saved as 24 bit RGB TIFF files, with 256 levels of intensity value for each colour channel. Images were then resized so that the distance from the centre of the macula to the temporal disc edge was 490 pixels, allowing uniformity of processing. The regions studied were the central 1000 μm diameter circular subfield and the 1000–3000 μm diameter annular subfield centred on the fovea, the central, and middle subfields defined by the Wisconsin grading template. Drusen area was measured as a percentage of the 1000 μm and 3000 μm subfield, and was unaffected by variable image size. The variation in brightness found in most fundus photographs was normalised using the red, green, and blue channels to create a standardised image in Photoshop, with nearly identical mean background colours, establishing a uniform basis for drusen segmentation. Contrast enhanced versions of the images (Photoshop/autolevels) were created for ease of visual recognition of drusen. Drusen analysis was carried out on the green channel of the standardised image using a digital template.

After background levelling, the optimum threshold level for drusen segmentation in the selected subfield is chosen by flicker comparison with the contrast enhanced image. For a given threshold, the drusen image is segmented such that pixels with brightness intensities above the threshold are coloured green, to label as drusen, and the rest darkened. Each such drusen image is superimposed on the contrast enhanced image. The optimised threshold is selected by visually inspecting the correspondence of the boundaries of the segmented drusen objects to those of the contrast enhanced objects. The threshold is then adjusted so that this visual fit is optimum in the aggregate as judged by the user (fig 1A–C). The total drusen area as a percentage of the selected subfield is then read directly (Photoshop/Histogram).

As part of the interinstitutional study, one expert and one non-expert grader from each institution (Eye Institute, Columbia University, USA and Kings College Hospital, London (KCH)) independently performed drusen quantification on the 10 images. A random effect ANOVA was used to assess the interobserver agreement in terms of the intraclass correlation coefficient (ICC). The interobserver and interinstitutional results were fitted in a random intercept (mixed) model.
linear model in order to determine if the two institutions were related to any measure disagreement. The automated measurements were also compared against the stereo manual grading and the difference was estimated using the method suggested by Bland and Altman.14

Secondly, as part of a pretrial assessment for a potential drusen reduction randomised controlled trial, 100 consecutive fluorescein angiograms taken at KCH between April 1999 and November 2002 were reviewed. Patients included had choroidal neovascularisation as a result of AMD in one eye and significant drusen in the fellow eye (defined as five large drusen or more than 20 small drusen in the macular area). Colour images of the fellow eye were analysed to determine whether they were suitable to be assessed by this software based on its previously determined limitations.13

RESULTS
Interinstitutional validation
The most labour intensive process in our method was in background levelling. For simple images this took about 1 minute and for more complicated images about 7 minutes. The total time taken for complete image evaluation and drusen segmentation varied from 4–10 minutes compared to 20–30 minutes per image with manual tracing.

There was good consensus between graders in the selection of the final threshold for drusen quantification. The random effects ANOVA showed a high degree of interobserver agreement as most of the variability was due to the interpatient variation (F (9,30) = 20; p = 0.00001 and F (9,30) = 22; p = 0.00001 for the central and middle subfields). Although the results were rather similar for the middle and central subfields, the middle subfield showed better agreement in general. The ICC for interobserver reliability was 0.83 (95% CI: 67 to 95) for the central subfield and 0.84 (95% CI: 69 to 99) for the middle subfield. The random effects linear mixed model confirmed good interobserver agreement (mean difference of 4.7; 95% CI: −7 to 17.6; p = 0.44 3.6; 95% CI: −2.4 to 9.6; p = 0.24, for the central and middle subfields), and, in addition, it showed a non-significant disagreement between the two countries.

When the automated grading results were compared to the manual stereo grading results, we found that the automated measures tended to underestimate for large drusen values in both subfields. In addition, in the central subfield, the automated measures tended to overestimate for smaller drusen values. Optimum agreement with manual grading was obtained when the percentage of drusen in the measured area was 25%. Overall agreement with the manual grading results remained good and the within patient coefficient of variation was about 20% for all the pairwise comparisons. Figure 2A shows the plot of the automated versus manual measurements for each observer for the middle subfield, with the line of equality for comparison. The Bland and Altman plots of the difference versus mean of the automated and manual measurements for each observer are presented in Figure 2B. The estimates of the disagreements between

Figure 1  Images illustrating drusen segmentation. Contrast enhanced layer for drusen identification (A), selection of best fit threshold (B), alternative threshold over representing drusen load (C).

Figure 2  (A) Plots of the automated v manual measurements in relation to the line of equality for each observer (middle subfield). (B) Difference v mean of automated and manual measurements for each observer (middle subfield).
automated and manual gradings for each observer are shown in Table 1, together with the test of whether the disagreement was significantly different from zero, either overestimating or underestimating the true drusen value. There was no significant deviation from the manual gradings for the central subfields for all four graders. Underestimation of drusen levels in the middle subfield reached significance for grader RTS.

### Practical applicability

Seventy nine images were found to be suitable for analysis by the software. Of the 21 considered unsuitable, 13 had extensive mixed retinal pigment epithelial (RPE) changes limiting drusen identification (fig 3A). Five had a significant number of reticular drusen, which are poorly identified (fig 3B), and three had multiple small areas of RPE atrophy, which are difficult to distinguish from drusen (fig 3C). Significant thinning of RPE with baring of choroidal vessels can also make drusen recognition difficult (fig 3D).

### CONCLUSION

Previous attempts at automated quantification have had limitations.15–17 Shin et al described a method of computer assisted, interactive image processing which afforded higher accuracy.18 They achieved an ICC of 0.92 and 0.93 for comparison of expert manual grading with automated supervised grading by two observers. However, major problems included identification of soft drusen with indistinct borders, large size drusen, and contrast confusion from darker blood vessels.

Comparison of the results of our semiautomated method with stereo manual grading and intraobserver reproducibility have been reported previously.13 Good interobserver reproducibility has been demonstrated in the present study by graders from two institutions. Our digital method requires two supervised steps which are potential sources of interobserver variation—firstly, in background levelling for uniformity of drusen analysis and, secondly, in the selection of the threshold for drusen quantification. Levelling of the macular background is an approximation that may make a given section too bright or too dim. Consequently, drusen would be over-represented or under-represented. This was not a significant source of variation in this study. Disagreements between graders were predominantly the result of the subjective choice of final threshold selection. Large amounts of soft drusen with indistinct borders were more likely to be underestimated. Also, drusen underlying mixed RPE changes could potentially be excluded. Poor image quality and lack of stereo caused a tendency to include RPE atrophy as drusen. These confounding factors would have to be removed manually or by additional software and are a source of potential interinstitutional and interobserver variation.

Although a semiautomated method requires greater time from the grader than a fully automatic system, it is an acceptable compromise for improved accuracy and reproducibility in relation to some published fully automated methods.19 Rapantzikos et al have had greater success using a histogram based adaptive local thresholding.20 However the limitations of confounding lesions has not been explored. Our semiautomated software has the potential to assess the change of drusen area in the majority of high risk patients with AMD. It has value in trials of drusen dynamics and reduction.

### Table 1

<table>
<thead>
<tr>
<th>Observer</th>
<th>Central subfield</th>
<th>Middle subfield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disagreement in relation to stereo grading (observer manual)</td>
<td>95% CI</td>
</tr>
<tr>
<td>JC</td>
<td>6.3</td>
<td>−4.7 to 17</td>
</tr>
<tr>
<td>RTS</td>
<td>5.2</td>
<td>−6.9 to 17</td>
</tr>
<tr>
<td>BL</td>
<td>8.5</td>
<td>−8 to 25</td>
</tr>
<tr>
<td>VS</td>
<td>6.8</td>
<td>(−9 to 23)</td>
</tr>
</tbody>
</table>

Figure 3  Images illustrating limitations of the practical application of software. Extensive RPE changes (A), reticular drusen (B), mixed drusen and RPE atrophy (C), baring of choroidal vessels (D).
Semiautomated drusen quantification

Authors’ affiliations
V Sivagnanavel, G B Lau, N V Chong, Retinal Research Unit, King’s College Hospital, University of London, UK
R T Smith, J Chan, Department of Ophthalmology, Columbia University, New York, NY, USA
C Donaldson, Department of Biostatistics, Research and Development, Kings College Hospital, University of London, UK

Support: NY Community Trust, King’s Ophthalmic Fund.

A part of these results was presented as posters at the Association for Research in Vision and Ophthalmology, Fort Lauderdale, 2003 and in abstract form in Invest Ophthalmol Vis Sci 2003;44:E-3654 and Invest Ophthalmol Vis Sci 2003;44:E-5002.

Correspondence to: Miss V Sivagnanavel, Retinal Research Unit, King’s College Hospital, University of London, UK, vasuki_siva1@yahoo.co.uk

Accepted for publication 29 September 2004

REFERENCES
Radial optic neurotomy for ischaemic central vein occlusion


Background/aims: Ischaemic central retinal vein occlusion (CRVO) accounts for 20–50% of all CRVO. No treatment has been proved to be effective. The efficacy of radial optic neurotomy (RON) was evaluated in eyes with ischaemic CRVO.

Methods: 10 patients with ischaemic CRVO underwent RON. After pars plana vitrectomy, a microvitreoretinal blade was used to incise the scleral ring, cribiform plate, and adjacent sclera at the nasal edge of the optic disc. Best corrected visual acuity (BCVA), intraocular pressure (IOP), fluorescein angiography (FA), multifocal electroretinography (mERG), and optical coherence tomography (OCT) were measured preoperatively and at 1, 3, and 6 months postoperatively.

Results: No visual improvement was noted in the eyes that underwent RON. FA and mERG showed no increase in retinal perfusion or retinal function postoperatively. Mean macular thickness was measured from 841 (SD 170) μm preoperatively to 162 (SD 34) μm at the sixth postoperative month. One patient had retinal central artery perforation postoperatively. One patient developed neovascular glaucoma.

Conclusion: RON in ischaemic CRVO did not improve visual function (by mERG) or visual acuity although macular thickness did improve. This technique may be associated with potential risks. Randomised studies are needed to corroborate these results.

Central retinal vein occlusion (CRVO) is a frequent cause of visual loss for which no effective and reliable form of treatment is currently available. Although the aetiology and pathogenesis are not completely understood, thrombus of the central retinal vein in the area of the lamina cribrosa is thought to be involved in the pathophysiology of CRVO. Various treatments have been suggested for CRVO, but, to date, none has been effective in addressing the underlying pathogenesis. Iris neovascularisation and neovascular glaucoma may occur in 43–85% of ischaemic CRVO. Panretinal laser photocoagulation can reduce neovascular complications associated with CRVO. Grid macular laser photocoagulation was found to decrease the amount of macular oedema but did not improve visual acuities in patients with CRVO. Laser induced chorioretinal venous anastomosis has been advocated to improve vision in non-ischaemic CRVO. Radial optic neurotomy has also been shown to be beneficial for the treatment of CRVO. The exact mechanism is not known, but the procedure is thought to decompress the lumen of the central retinal vein and may induce opticociliary venous anastomosis or retinochorial shunts. Moreover, pars plana vitrectomy is thought to increase oxygenation to the retina and to reduce the risk of retinal neovascularisation.

The efficacy of radial optic neurotomy (RON) in cases of ischaemic CRVO has not been established. The purpose of this study was to address the safety and effect of pars plana vitrectomy combined with RON in ischaemic CRVO.

METHODS

Ten consecutive patients with ischaemic CRVO referred to Hospital Luis Sanchez Bulnes, Asociación para Evitar la Ceguera en México, were included in this non-comparative, prospective series. The study was approved by hospital review committee. The inclusion criteria were age ≥ 21 years old, confirmed presence of CRVO, less than 6 months’ evolution with visual acuity (VA) of < 20/100, over 10 disc areas of non-perfused retina by fluorescein angiography (FA), intraocular pressure ≤ 21 mm Hg, afferent pupillary defect, ability to obtain good quality fundus photographs and angiograms, and absence of neovascularisation. The exclusion criteria in the study eye were intercurrent eye disease that is likely to affect VA over the study period, presence of any diabetic retinopathy, other retinal vascular disease, vitreous haemorrhage, presence of neovascularisation (iris, angle, retina, and disc) or previous laser treatment. Best corrected ETDRS visual acuity, pupillary examination, slit lamp examination, indirect ophthalmoscopy, fundus photography, multifocal electroretinography (mERG), optical coherence tomography (OCT), and FA were performed preoperatively and at 1, 3, and 6 months postoperatively. Visual acuity improvement or decrease was defined as a difference of two or more lines from baseline.

Surgical procedure

After informed consent was obtained, patients underwent a standard three port pars plana vitrectomy during which the posterior hyaloid was detached and removed. Intraoperatively, a site on the nasal edge of the disc was identified which avoided the major retinal vessels. RON was performed in a radial fashion to avoid transecting nerve fibres. A specially designed 20 gauge microvitreoretinal blade was inserted to a depth of 2.5 mm as described by Opremcak, et al. If bleeding was observed, the infusion bottle was raised to stop the haemorrhage. The sclerotomy sites and conjunctiva were closed in the usual fashion. No gas tamponade was used.

OCT and mERG

Macular thickness was analysed with OCT (Humphrey 1000; Humphrey Instruments, San Leandro, CA, USA). Measurement of macular thickness was done according to the protocol of Hee et al., in which six consecutive radial tomographic scans, at the centre of the fovea at equal angular distances were obtained. The central foveal thickness was determined.

Abbreviations: BCVA, best corrected visual acuity; CRVO, central retinal vein occlusion; FA, fluorescein angiography; mERG, multifocal electroretinography; OCT, optical coherence tomography; RON, radial optic neurotomy; VA, visual acuity
determined by the average measurements in the central 500 µm around the intersection of the six cuts (macular fast scan program).

The electrical function of the macular area was determined by mfERG. The RETI scan multifocal system (Roland Consult) was used for this purpose. The stimulation and recording of the mfERG were performed using the m-sequence technique. Contact lens ERG-JET electrodes as well as one ground electrode in the centre of forehead, and two temporal reference electrodes were positioned. The stimulus, consisting of 61 hexagons covering a visual field of 30°, was presented on a monitor (ELSA 200 VGA monitor) with a frame rate of 75 Hz at a distance of 28 cm from the patient’s eye. Each element alternated between black and white (93% contrast, mean luminance 51.8 cd/m²). The patient was instructed to maintain fixation on longitudinal axes intersecting one focal point. The amplifier setting was 100 mV; the lower cut-off frequency was 10 Hz and the upper cut-off frequency was 100 Hz. No notch filter was used. Each recording session was subdivided into eight recording segments of approximately 47 seconds. The signals were registered with sampling intervals of 83 ms. The results were distributed in six consecutive rings where the N1 and P1 amplitudes, and the implicit times were obtained for each.

<table>
<thead>
<tr>
<th>Amplitudes b</th>
<th>Amplitudes b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 1 (A) Preoperative colour fundus photograph of case 1. (B) Fluorescein angiography reveals hypofluorescence by blockage and non-perfused areas. (C) The same patient 1 month after treatment with radial optic neurotomy with central retina artery perforation. More confluent retinal haemorrhages can be seen. (D) The angiogram shows an absence of retinal circulation.

Figure 2 (A) Preoperative multifocal electroretinogram of case 1 shows a diffuse reduction in N1 and P1 waves. (B) One month postoperatively, the responses are further depressed.
Density by mfERG (nV/deg²) changed from 28.38 (5.6) to 6 month postoperative measurements. The mean response follow up measured 679 (205).

Postoperative mean macular thickness at 1, 3, and 6 month (deg²). Statistical analysis of these measurable variables was done with a paired t test.

RESULTS

The study data are displayed in table 1. Seven male and three female patients were recruited. Mean age was 69.6 years (range 54–78 years) with mean follow up of 12 months (8–18 months). All patients were Hispanic. Mean duration of symptoms before surgery was 97.5 days (range 60–150 days). All patients had a relative afferent pupillary defect. None of our patients showed any change in BCVA. Mean intraocular pressure was 15.5 (SD 2.95) mm Hg preoperatively and 11.7 (1.05) mm Hg postoperatively. Fluorescein angiography showed no improvement in perfusion. Mean macular thickness (table 2) before surgery measured 841 (170) μm. Postoperative mean macular thickness at 1, 3, and 6 month follow up measured 679 (205) μm, 415 (176) μm, and 162 (34) μm, respectively (p < 0.001, between preoperative and 6 month postoperative measurements). The mean response density by mfERG (nV/deg²) changed from 28.38 (5.6) to 20.46 (7.8) (p = 0.005) (table 2 and fig 2). Patients with longer follow up showed no major changes. One eye developed iris neovascularisation postoperatively and panretinal photocoagulation was performed. One patient had central retinal artery perforation intraoperatively (fig 1). His postoperative FA displayed a total absence of retinal perfusion. Intraoperative bleeding occurred in two eyes and was controlled by raising the infusion bottle.

DISCUSSION

CRVO is the second most frequent vascular cause of visual loss after diabetic retinopathy.1

Thrombus formation at the cribriform plate may be a primary or secondary event in CRVO.1,10 Although CRVO may be caused by obstruction of the central retinal vein in the area of the lamina cribrosa, it has been proposed that a non-perfused CRVO is the result of compromised blood flow in the central artery and in the vein.11 The unique anatomy of the optic nerve has led to the hypothesis that CRVO is due to a “compartment syndrome” in which the CRV may be compressed generating turbulence and secondary thrombosis. Various treatments currently being evaluated include laser induced chorioretinal venous anastomosis,6 and recombinant tissue plasminogen activator given intravitreally7,12 or injected directly into a cannulated retinal vein.12 Because there is no effective treatment for CRVO, RON has been proposed to alleviate the “compartment syndrome.” External approaches to optic nerve decompression have been attempted in patients with CRVO with variable clinical results.13,14 The vitreoretinal approach, designed to relieve the “compartment syndrome” at the scleral outlet through an internal approach, may improve venous outflow in eyes with CRVO. Although controversial, this procedure has been reported to achieve good anatomical and visual results in patients with non-ischaemic and ischaemic CRVO.15 Opremcak et al reported a 73% incidence of rapid improvement of visual acuity with an average gain of five lines of vision. This study included patients with both ischaemic and non-ischaemic CRVO.4 Because of the relatively good visual prognosis of patients with non-ischaemic CRVO, we included only patients with ischaemic CRVO. Of our series, only two patients (20%) had a marginal (less than two lines) improvement of BCVA. They may have improved because of the vitrectomy itself or because of the natural history of CRVO. The Central Vein Occlusion Study showed that 20% of patients with initial visual acuity of less than 20/200 can improve to better than 20/200 3 years after the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics and visual acuity results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>Age (years)</td>
</tr>
<tr>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>67</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
</tr>
</tbody>
</table>

IOP, intraocular pressure; HM, hand motion; IP, light perception.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Results of macular thickness and complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>Central macular thickness (μm)</td>
</tr>
<tr>
<td></td>
<td>Preop</td>
</tr>
<tr>
<td>1</td>
<td>900</td>
</tr>
<tr>
<td>2</td>
<td>900</td>
</tr>
<tr>
<td>3</td>
<td>739</td>
</tr>
<tr>
<td>4</td>
<td>900</td>
</tr>
<tr>
<td>5</td>
<td>670</td>
</tr>
<tr>
<td>6</td>
<td>611</td>
</tr>
<tr>
<td>7</td>
<td>900</td>
</tr>
<tr>
<td>8</td>
<td>1200</td>
</tr>
<tr>
<td>9</td>
<td>900</td>
</tr>
<tr>
<td>10</td>
<td>690</td>
</tr>
</tbody>
</table>

OCT, optical coherence tomography; PO 1m, postoperative at 1 month; PO 3m, postoperative at 3 months; PO 6m, postoperative at 6 months; CRA, central retinal artery.
occlusive event. Perfusion status in FA did not improve after RON in our study. Macular oedema improved by OCT in all patients but did not correlate with improvement of the visual acuity. This correlates well with the findings of the Central Vein Occlusion Study, where despite resolution of macular oedema following grid laser treatment, visual acuity did not improve. Macular function by mERG 6 month postoperatively showed a reduction in P1 mean response in all patients. All this might reflect the ischaemic status of the macula.

Williamson et al. reported that pars plana vitrectomy is a safe procedure in ischaemic CRVO and that, combined with gas, it could lower the risk of neovascular glaucoma.

In our study, only one patient developed iris neovascularisation (as opposed to 36% in CVOS). Although we cannot explain this low incidence we believe that pars plana vitrectomy somehow may improve vitreous cavity oxygenation reducing the neovascular stimulus. The possibility of serious complications cannot be overlooked. Creating an incision at the edge of the optic nerve carries a potential risk of laceration of the central retinal artery (as occurred in one of our patients) or vein, optic nerve fibre damage with visual field loss; globe perforation, and retinal detachment. In patients who present with oedema of the optic disc, it becomes very difficult to define the exact site where the incision is to be performed increasing such risks.

The efficacy and safety of RON is still in question. Further studies such as a randomised controlled clinical trial are needed to determine whether RON is of benefit in ischaemic CRVO. Our results suggest that eyes with ischaemic CRVO do not benefit from this procedure.

References

Optical coherence tomography characterisation of idiopathic central serous chorioretinopathy

J A Montero, J M Ruiz-Moreno

Aim: To describe retinal findings in patients with idiopathic central serous chorioretinopathy (ICSC) as assessed by optical coherence tomography (OCT), and to compare them to fluorescein angiography (FA) findings.

Methods: Case series of 39 eyes from 36 patients with ICSC. Complete ophthalmological examination, last generation OCT (StratusOCT, Software version 3.1) and FA were performed. Six radial scans using OCT were performed and repeated. Singular findings were recorded, OCT images were measured and the results compared with those of FA. The main outcome measures were FA and OCT findings.

Results: Two patterns of distinct OCT findings are described. In the first one, an optically empty vaulted area of different heights was observed under the neurosensory retina in 36 eyes, being related to fluorescein filled areas; in 35 of them, highly characteristic small bulges could be observed protruding from the retinal pigment epithelium (RPE), angiographically related to leaking spots. In the second pattern, three eyes showed an almost semicircular space under the RPE, with thinner overlying retina.

Conclusions: OCT may offer a new approach to the staging and knowledge of ICSC, and may help the understanding of the mechanisms of the disease.

Diopathic central serous chorioretinopathy (ICSC) typically affects young and middle aged males in their third to fifth decades. Patients may develop one or more small areas of serous detachment of retinal pigment epithelium (RPE) in the macula or in the paramacular area, which may be followed by serous detachment of the overlying and surrounding retina. Demonstration of ICSC is based on angiographic pooling of subretinal fluid, appearance of defects in the RPE, and typical dye leakage from the choroid into the subretinal space.1,2

New diagnostic and therapeutic tools have increased our ability to study this condition, allowing us to have new theories on its in-depth mechanisms or the presence of choroidal neovascularisation (CNV).3,4 Optical coherence tomography (OCT) is an imaging procedure that uses reflection of light off the retinal layers to create a false colour tomographic image of retinal and RPE structures with a resolution of 10 μm axially and 20 μm in transverse dimension.5

Methods

We performed OCT (StratusOCT Software 3.1, Carl Zeiss Meditec Inc, San Leandro, CA, USA) and fluorescein angiography (FA) (Imagenet 2000, Topcon TRC50IX, Topcon Corp, Japan) on 39 eyes from 36 consecutive patients with ICSC. OCT and FA were performed on the same day.

Eleven patients (10 males, one female, 13 eyes) had had symptomatic ICSC with angiographic changes for more than 12 months without clinical normalisation (chronic forms). Fifteen patients (11 males and four females, 15 eyes) have had the first episode for less than 4 months (acute forms). Ten patients (six males and four females, 11 eyes) have had two or more episodes.

OCT was performed by acquiring six radial scans, 6 mm long, centred in the fovea using the fast macular scan function (transverse sampling, 128 A-scans). When fixation was poor, scans were centred in the fovea under video surveillance. OCT scans were repeated three times to ensure reproducibility. When particular details were observed, the scan was centred in that location to check that they were not caused by saccadic movements or other artefacts, at a higher scan rate (transverse sampling, 512 A-scans).

Scans were examined and compared to FA to determine the mutual relation and nature of the findings. OCT video imaging was used to centre scans on angiographic photographs to locate and identify the findings on FA. Retinal thickness was measured at the fovea using the macular thickness calliper.

Results

The mean age of the patients was 43 (SD 8) years, (range 29–68), with 27 males (75%) and nine females (25%). All were white. Mean visual acuity at baseline was 20/25 (range 20/20 to 20/60). Fundus examination showed serous detachment in all of them with patches of RPE atrophy. No haemorrhages or choroidal neovascularisation (CNV) were observed.

OCT showed foveal distortion and cystic and atrophic macular changes in all eyes. Thirty six eyes (92%) showed neuroretinal detachments corresponding to the affected area, with empty spaces underneath. Three eyes (8%) showed RPE detachment and overlying retinal thinning.

Two different patterns could be observed. The first pattern was an empty vaulted area of variable height (41–539 μm, mean 198 μm, SD 107) under the neurosensory retina, angiographically related to fluorescein filled areas. It was present on 36 eyes (15 from acute forms 100%, 11 from multip episodic forms 100%, and 10 from chronic forms 77%). Empty spaces were underlined by a hyper-reflective line, probably corresponding to scarred RPE. In 35 eyes a small bulge was observed protruding from RPE (fig 2A–D). Foveal thickness was 135–268 μm (mean 207 μm, SD 34). In four cases the cystic space was very

Abbreviations: CNV, choroidal neovascularisation; FA, fluorescein angiography; ICSC, idiopathic central serous chorioretinopathy; OCT, optical coherence tomography; PDT, photodynamic therapy; RPE, retinal pigment epithelium
shallow (fig 1D), showing the previously described bulge. Only one case showed one small cystic structure with an empty core, which might be assimilated to a small cystic RPE detachment.

Three eyes (all from chronic forms, 23%) showed a vaulted space of variable height (fig 1E, F) under RPE, what probably identifies them as RPE detachments. Overlying retina measured 83–145 μm (mean 106 μm, SD 36). Angiographic correspondence of these structures was actually RPE detachments (fig 2D and E).

FA showed fluorescein pooling under detached retina in all cases. Thirty six eyes (92%) showed active forms of ICSC. Leaking points and smokestacks could be demonstrated in 28 eyes (72%) (fig 2A–D); meanwhile eight eyes (20%) showed diffuse patterns with severe, diffuse RPE atrophy (fig 2E and F). One eye (3%) showed only RPE defects. All eyes showed parafoveal, patchy RPE atrophy without CNV.

Comparing OCT scans with FA it could be demonstrated that protrusions were located exactly where fluorescein leakage appeared. A similar topographic relation could be established for RPE detachments.

DISCUSSION

The role of OCT as a non-invasive way of studying the retina is well known.3 5 6–10 Several papers have recently appeared describing OCT findings in eyes with ICSC.3 8–14

We describe two different OCT patterns in patients with ICSC, and one finding highly characteristic of this condition. Acute and multi-episodic forms of ICSC showed in all cases empty subretinal spaces. In most of them bulges protruded from the RPE under a detached retina; this also appears in some chronic cases, which probably meant activity of the disease. Their location was that of the angiographic leakage.

The appearance of high, vaulted subretinal spaces in OCT was associated with the biomicroscopical presence of local neuroretinal detachment and fluorescein filled areas. Bulges could not be located biomicroscopically.

Twenty three per cent of chronic forms appeared to be associated with high RPE detachments and retinal thinning without retinal detachment. FA showed progressive filling. Biomicroscopically they showed well defined neuroretinal detachment.

Kampeter and Jonas5 and Drexler et al9 have previously described similar findings lacking hyper-reflective RPE, considering them to be RPE detachments. Drexler et al were uncertain whether these findings might actually be
arteFACTual. We cannot consider these bulges as RPE detachments since RPE seemed to be still adhered under them, nor artefactual because they are reproducible and correlate with FA leaking points. We would rather consider them RPE protrusions, or thickening.

Different findings have been described in eyes with ICSC.13 14 Wang et al15 described retinal thinning ranging from 51–74% of normal fovea in patients with longer lasting ICSC. Iida et al16 described retinal thickening as retinal oedema similar to what is found in patients with CNV associated with AMD.17 18 In our series, retinal thickness observed during the acute phase is not much different from that of healthy volunteers (219.8 μm), and was clearly inferior to what is found in patients with active CNV (289.9 (SD 92.1) μm).15 It must be also borne in mind that different software and hardware were used in Iida’s work,16 which may also contribute to the different absolute measurements.

ICSC is considered a multifactorial disease in which focal defects of RPE origin leak into the subtretinal space, and there are secondary RPE and retinal changes.19 The mechanism of ICSC is highly controversial.20 RPE scrous detachment appears at early phases, and usually can be angiographically identified as a leaking point.1 RPE detachment is usually associated to serous detachment of the overlying retina. Some attempts have been made to treat ICSC by photo-dynamic therapy (PDT).1 21

Pathological material is limited. Serous macular detachment has been pathologically described, with and without defects or detachment of the RPE.1

Ultrastructural studies in animal models of ICSC have shown defects in RPE, which might favour a breakdown in the outer blood-retinal barrier.22 The issue is whether the bulges we describe are local RPE abnormalities related to FA leakage and to the pathophysiology of ICSC, or artefacts. We consider that the close topographic correspondence of these structures in FA and OCT suggest they are probably involved in the mechanism of the condition. We have found them in 35 of 39 eyes with ICSC (90%), but not in more than 1800 patients (more than 2600 eyes) with conditions different from ICSC (normal, CNV, uveitis, macular oedema, optic disc pit, etc). They might represent minimal RPE detachments, or focal defects of RPE.

Chronic forms were associated with retinal thinning and highly vaulted RPE detachments like those described by Kampfetter and Jonas23 and Drexler et al.9 The persistence of retinal fluid may induce retinal cystoid changes and thinning, mainly in chronic or recurrent forms.1

Considering ICSC angiographic patterns (hot spot 72%, diffuse RPE atrophy in up to 90% of cases), OCT seems to be more sensitive to give a diagnosis (bulge 90%, focal neuroretinal or RPE detachment up to 100%), and to evaluate the degree of activity of ICSC, and is not influenced by the degree of RPE atrophy. It also provides an easier differential diagnosis from other conditions which might be similar by biomicroscope and FA (such as age related macular degeneration). OCT is safer and less time consuming than FA, and can be repeated more often.

OCT may offer a new approach to the diagnosis and evaluation of retinal damage in ICSC, and help us to understand its staging and mechanisms.

Authors’ affiliations
J A Montero, J M Ruiz-Moreno, Instituto Oftalmológico de Alicante, Vitreo-Retinal Unit, Alicante, Spain
J M Ruiz-Moreno, Department of Ophthalmology, Miguel Hernández University School of Medicine, Alicante, Spain
The authors have no financial interest in the devices and procedures described.

Correspondence to: Javier A Montero, Instituto Oftalmológico de Alicante, Avenida de Denia 111, 03015, Alicante, Spain; msm02va@wanadoo.es

Accepted for publication 1 October 2004

REFERENCES

www.bjophthalmol.com
Background/aims: The success of the treatment in patients with retinopathy of prematurity (ROP) is mainly associated with timely diagnosis and appropriate management. Information dissemination is crucial for the outcome of ROP. This study aimed to evaluate the quality of the information about ROP available for patients on the internet.

Methods: Cross sectional study. In March 2004 the ROP information available on the internet was evaluated using two search engines (MetaCrawler and MSN) and four key terms ("retinopathy of prematurity," "premature eye," "premature retina," and "ROP"). The quality of each website was evaluated using a score system. The sites were classified as academic, organisational, or commercial. Readability, general quality of the website (based on ownership, purpose, authorship, author qualification, attribution, interactivity, and currency), and quality of the content specific to ROP (definition, causes, epidemiology, risk factors, diagnosis, classification, treatment, and prognosis) were analysed.

Results: Of 114 websites evaluated, 40 were included. 10 sites (25.0%) were academic, eight (20.0%) organisational, and 22 (55.0%) commercial. In the majority of the sites (62.5%) the ROP information was fair or poor.

Conclusions: A large amount of information about ROP is available on the internet. However, most websites were considered incomplete.


Table 1 Quality component scoring system

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ownership</td>
<td></td>
</tr>
<tr>
<td>No indication of ownership/sponsorship</td>
<td>0</td>
</tr>
<tr>
<td>Ownership/sponsorship clearly stated</td>
<td>1</td>
</tr>
<tr>
<td>Purpose grading</td>
<td></td>
</tr>
<tr>
<td>No statement of purpose</td>
<td>0</td>
</tr>
<tr>
<td>Purpose stated as educational but the financial profit from use of the site exists</td>
<td>1</td>
</tr>
<tr>
<td>Distinction is made as to whether the information provided is for commercial purposes or educational purposes, or both</td>
<td>2</td>
</tr>
<tr>
<td>Authorship</td>
<td></td>
</tr>
<tr>
<td>No indication of authorship</td>
<td>0</td>
</tr>
<tr>
<td>All other indications of authorship</td>
<td>1</td>
</tr>
<tr>
<td>Name of person(s) supplying information clearly provided</td>
<td>2</td>
</tr>
<tr>
<td>Author qualification grading</td>
<td></td>
</tr>
<tr>
<td>Author has no officially recognised experience in the field or no such information is provided</td>
<td>0</td>
</tr>
<tr>
<td>Information about the author’s professional qualification is vague, or if the author has no professional experience but has direct personal experience (ROP patient)</td>
<td>1</td>
</tr>
<tr>
<td>If author is a healthcare professional</td>
<td>2</td>
</tr>
<tr>
<td>Attribution</td>
<td></td>
</tr>
<tr>
<td>No references provided for requiring statements</td>
<td>0</td>
</tr>
<tr>
<td>References are provided for some, but not all, statements requiring factual information</td>
<td>1</td>
</tr>
<tr>
<td>Attribution for all statements conveying factual information is present</td>
<td>2</td>
</tr>
<tr>
<td>Interactivity</td>
<td></td>
</tr>
<tr>
<td>No contact provided</td>
<td>0</td>
</tr>
<tr>
<td>Telephone number, email, or mailing address provided</td>
<td>1</td>
</tr>
<tr>
<td>Clear invitation to comment or ask questions by an email address or link to a form</td>
<td>2</td>
</tr>
<tr>
<td>Currency</td>
<td></td>
</tr>
<tr>
<td>No date provided</td>
<td>0</td>
</tr>
<tr>
<td>Date of original posting, but no information about the date of last revision or frequency of updates</td>
<td>1</td>
</tr>
<tr>
<td>Date of original posting and date of last revision or frequency of updates clearly stated</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: ROP, retinopathy of prematurity
Modifications were made in applying the previously tested foundation code principles was used. Necessary medical site evaluation and on the Health On The Net A score system based on those previously determined for Quality word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word.

Site evaluation was divided into readability, quality, and technical.

Readability
To determine the site readability, we copied the ROP material from each site, pasted it into a Microsoft Word document (Microsoft Office, 2000), and obtained the Flesch-Kincaid grade level score. This score rates text on US school grade levels or years (range third to 12th grade) and it is based on the average of sentence length and number of syllables per word. A score of 8.0 or less is the recommended level for standard documents.

Quality
A score system based on those previously determined for medical site evaluation and on the Health On The Net foundation code principles was used. Necessary medical site evaluation and on the Health On The Net A score system based on those previously determined for Quality word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word. A score of 8.0 or less is the recommended level for the average of sentence length and number of syllables per word.

Website classification was performed only after quality, technical, and readability data were acquired.

Statistical analysis
Scores for each site were converted to a percentage value of the maximum range. Based on the overall percentage score, a label was assigned to each site as described previously: excellent (≥80%), very good (70% to 79%), good (60% to 69%), fair (50% to 59%), and poor (<49%).

One way ANOVA was used to compare percentage scores. Spearman correlation was used to analyse readability, quality, and technical scores. A p value of <0.05 was considered significant.

RESULTS
For each heading search, a range of 73 to 151 101 sites was listed. The first 30 sites were reviewed (240 sites), but because the searches sometimes discovered the same sites, only 114 unique sites were retrieved. A total of 74 (64.9%) sites were excluded because the information contained was not related to ROP (43 websites), the information was aimed at healthcare professionals (24 sites), the site provided only links to other sites (two sites), or to have access to the page a fee or registration was required (two sites). Of the 40 sites evaluated, 10 (25.0%) were classified as academic, eight (20.0%) as organisational, and 22 (55.0%) as commercial.

The mean overall percentage score was 59.1% (SD 17.4%). The mean quality percentage score was 54.8% (20.2%) and the mean technical percentage score was 62.6% (21.3%). The quality, technical, and overall percentage scores did not differ among the website groups (one way ANOVA; p = 0.664.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Technical component score system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>Definition of ROP</td>
</tr>
<tr>
<td></td>
<td>Causes of ROP</td>
</tr>
<tr>
<td></td>
<td>Epidemiology</td>
</tr>
<tr>
<td></td>
<td>Risk factors for ROP</td>
</tr>
<tr>
<td></td>
<td>How to diagnose ROP</td>
</tr>
<tr>
<td></td>
<td>Classification of ROP</td>
</tr>
<tr>
<td></td>
<td>Treatment of ROP</td>
</tr>
<tr>
<td></td>
<td>Prognosis of ROP</td>
</tr>
<tr>
<td>Score</td>
<td>0 = not discussed on the site, 1 = briefly explained on the site, 2 = comprehensively explained on the site.</td>
</tr>
</tbody>
</table>

Table 3: Quality and technical scores (2 is the best score) for ROP information on 40 websites

<table>
<thead>
<tr>
<th>Criteria</th>
<th>All sites (n = 40)</th>
<th>Academic (n = 10)</th>
<th>Organisational (n = 8)</th>
<th>Commercial (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ownership</td>
<td>87.5</td>
<td>100.0</td>
<td>87.5</td>
<td>90.9</td>
</tr>
<tr>
<td>Purpose</td>
<td>5.0</td>
<td>0.0</td>
<td>87.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Authorship</td>
<td>37.5</td>
<td>10.0</td>
<td>37.5</td>
<td>27.3</td>
</tr>
<tr>
<td>Author qualification</td>
<td>57.5</td>
<td>50.0</td>
<td>37.5</td>
<td>27.3</td>
</tr>
<tr>
<td>Attribution</td>
<td>20.0</td>
<td>10.0</td>
<td>25.0</td>
<td>27.3</td>
</tr>
<tr>
<td>Interactivity</td>
<td>20.0</td>
<td>10.0</td>
<td>25.0</td>
<td>27.3</td>
</tr>
<tr>
<td>Currency</td>
<td>5.0</td>
<td>10.0</td>
<td>62.5</td>
<td>27.3</td>
</tr>
<tr>
<td>Technical</td>
<td>82.5</td>
<td>90.0</td>
<td>87.5</td>
<td>73.3</td>
</tr>
<tr>
<td>Causes</td>
<td>72.5</td>
<td>10.0</td>
<td>75.0</td>
<td>18.2</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>25.0</td>
<td>30.0</td>
<td>50.0</td>
<td>34.6</td>
</tr>
<tr>
<td>Risk factors</td>
<td>42.5</td>
<td>10.0</td>
<td>37.5</td>
<td>40.9</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>22.5</td>
<td>10.0</td>
<td>37.5</td>
<td>45.5</td>
</tr>
<tr>
<td>Classification</td>
<td>30.0</td>
<td>50.0</td>
<td>75.0</td>
<td>27.3</td>
</tr>
<tr>
<td>Treatment</td>
<td>52.5</td>
<td>50.0</td>
<td>62.5</td>
<td>27.3</td>
</tr>
<tr>
<td>Prognosis</td>
<td>35.0</td>
<td>10.0</td>
<td>37.5</td>
<td>27.3</td>
</tr>
</tbody>
</table>

Values indicate the proportion of websites in each group, per criteria/score.

www.bjophthalmol.com
p = 0.129, p = 0.185, respectively). The proportion of each grading per criteria is presented in Table 3.

According to the overall percentage score, eight sites (20.0%) were considered excellent, three (7.5%) very good, four (10.0%) good, 10 (25.0%) fair, and 15 (37.5%) were poor. The rankings for sites in each of the three categories are provided in Table 4.

Clarity of the text was very variable between sites and most sites (95.0%) required a high “reading level.” The average Flesch-Kincaid grade level was 10.83 (or 10th grade, eighth month) with a standard deviation of plus or minus 1.33; 17 sites (42.5%) scored at the maximum readability, 12.0.

The quality score was correlated with the technical score (r = 0.4, p = 0.01). There was no correlation between the quality score and the readability level (r = 0.192, p = 0.236). There was a significant correlation between the technical score and the Flesch-Kincaid grade level (r = 0.372, p = 0.018), demonstrating that the sites providing better information related to ROP presented this using a more complex language.

**DISCUSSION**

We assessed the general quality, technical content, and readability of ROP information available on the internet. Although website evaluations were conducted by the same investigator, we consider that subjectivity was minimised by using well defined quantitative standard scores.

Overall, the majority of ROP sites were of poor or fair quality (62.5%). Similar results have been reported for health information websites addressing other diseases. Sites produced by organisations were better designed, with 62.5% of them presenting excellent, very good, or good quality information.

We observed a great variation in scores among the 40 analysed sites. In the general quality evaluation, a common flaw was the inadequate evidence of currency (95.0%), attribution (80.0%), and authorship (62.5%). These are important principles to ensure quality and reliability of site content. 

In the technical component of our evaluation, the most commonly omitted aspect was disease classification (50.0%). We consider that mentioning the classification helps parents to better understand the possible progression of the retinopathy to more complicated stages, often signifying poorer prognosis, highlighting the importance of the prompt treatment and adequate follow up. Another troubling finding is that 75.0% of the sites did not mention or adequately discuss the epidemiology of ROP or how the disease is detected (70.0%). These topics, in our opinion, should also receive special attention from website authors, as they can be important not only for the parents but also for the general physicians involved with premature babies.

The appropriateness of the language used in the website is also important. It is estimated that 20% of the adult population in the United States have low literacy skills or read below or at the fifth grade level. To ensure that the information is at an appropriate level for the general public the Flesch-Kincaid grade level ideally should be at the eighth level or below. In our study, however, 95% of the sites required a high reading level, with the sites presenting better ROP information using a more complex language.

Although an abundance of ROP information is available on the internet for patients and families, this study highlighted the poor quality of this information. Additionally, most patients who use this source of information do not have the background for evaluating the quality of the provided material. Therefore, it is important that ophthalmologists help to develop good quality websites and to ensure that their patients are directed to sites that provide accurate information.

Preparing and providing a list of “approved” sites for patients, or a list of “tips” on how to evaluate the general quality of a site (for example, currency, authorship), or even asking the patient about information they found on the internet and possible questions about it are means to guarantee that your patient will be benefit from the internet resources.

**Authors’ affiliations**

**E N Martins**, Department of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil

**E N Martins, L S Morse**, Department of Ophthalmology, University of California-Davis, Sacramento, CA, USA

Funding: This work was supported in part by an unrestricted grant to the Ophthalmology Department University of California, Davis from Research to Prevent Blindness, Inc, New York, NY, USA.

Competing interests: none declared

Correspondence to: Lawrence S Morse, MD, PhD, Department of Ophthalmology, University of California-Davis, 4860 Y Street, Suite 2400, Sacramento, CA 95817, USA; lsmorse@ucdavis.edu

Accepted for publication 6 October 2004

**REFERENCES**


14 Ohio State University. Revising and editing with Word: spelling, grammar, and style. Available at ccl.english.ohio-state.edu/handouts/miscellaneous/word_revision_spelling_grammar_pc.htm, accessed 12 April 2004.
Threshold Amsler grid as a screening tool for asymptomatic patients on hydroxychloroquine therapy

A Almony, S Garg, R K Peters, R Mamet, J Tsong, B Shibuya, R Kitridou, A A Sadun

Background/aims: Patients taking hydroxychloroquine (HCQ) are at risk of developing classic bull’s eye maculopathy. Currently, the standard Amsler grid (AG) is one of the most useful methods to identify such lesions. However, AG is a suprathreshold target and may not detect relative central scotomas. The aim of this study was to determine if the threshold Amsler grid (TAG) test, which varies light transmission through two cross polarising filters, allows increased detection of scotomas caused by HCQ toxicity.

Methods: 56 rheumatological patients taking HCQ and 12 similar patients not taking HCQ were tested by AG, red Amsler grid (RAG), and TAG.

Results: No scotomas were observed in patients never treated with HCQ. Among patients who had been treated with HCQ, AG revealed scotomas in two of 56 (3.64%) patients; in contrast, six (10.7%) and 37 (66.1%) scotomas were identified by RAG and TAG testing respectively. Additionally, the average area of each scotoma detected by all three methods expanded from 34.5 square degrees of central field loss on AG testing to 71 square degrees on RAG and 117 on TAG.

Conclusion: By decreasing the perceived luminance of the suprathreshold AG, TAG testing provides a novel alternative to detect shallow scotomas and areas of depressed retinal activity secondary to HCQ toxicity.

The 4-aminoquinolone compounds, chloroquine and hydroxychloroquine sulfate (HCQ), have long been used to treat connective tissue disorders, most specifically rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Currently, HCQ, which is far less toxic than chloroquine, continues to be used as an antimalarial drug and in the treatment of connective tissue diseases worldwide. Amsler grid (AG) testing has been a standard means of assessing the central visual field since its introduction in 1947 and a valuable screening method in order to prevent the sometimes irreversible manifestations of ocular toxicity. However, AG provides a suprathreshold target to examine the central visual field and relative scotomas may go undetected before they become absolute scotomas. In contra-distinction, threshold Amsler grid (TAG) varies perceived luminance by implementing the use of cross polarising filters, thereby decreasing the image contrast and serving as a more sensitive test to detect relative scotomas and depressions in patients with maculopathy.1-3 (fig 1)

The aim of this study was to determine if TAG testing allows early and increased sensitivity in the detection of scotomas caused by HCQ toxicity.

PATIENTS AND METHODS

Upon receiving institutional review board (IRB) approval for our study, we recruited patients from the rheumatology outpatient clinic at LA County USC in Los Angeles and obtained informed consent from them before study enrolment. All 77 individuals who were approached agreed to participate in this study.

The inclusion criteria were consecutive patients seen from 18 June 2002 to 25 July 2002 in the LA County-USC rheumatology outpatient clinic with a known history of connective tissue disorder and a best corrected visual acuity of at least 20/50. Patients with other disorders that might produce a maculopathy including diabetes mellitus, a history of ocular trauma, or other ocular disorders were excluded retrospectively (n = 7). Patients on other medications that might produce retinal toxicity including digoxin were also excluded (n = 1). One patient did not complete the study because she developed a headache during the examination. Of the remaining 68 patients, 56 (82.4%) were taking HCQ for their connective tissue disorder. The 12 patients who were not taking HCQ had never taken it and served as controls.

Data were collected from the patients’ medical charts and corroborated with the patient in a written questionnaire regarding date of birth, sex, ethnicity, diagnosis of connective tissue disorder, HCQ dose and duration, current medications, history of digoxin use, medical and surgical history, ocular history, and baseline and follow up ophthalmological.

Abbreviations: AG, Amsler grid; HCQ, hydroxychloroquine; RA, rheumatoid arthritis; RAG, red Amsler grid; SLE, systemic lupus erythematosus; TAG, threshold Amsler grid
examinations (patients at LAC-USC are referred for a complete baseline ophthalmological examination before starting HCQ therapy which includes a dilated retina examination and central visual field sensitivity testing by an Amsler grid as well as complete annual ophthalmological follow up examinations). In the questionnaire, patients were also asked to report any visual complaints. Each patient was weighed during the examination.

For all patients, each eye was tested separately using five examinations while the untested eye remained occluded. Each patient received an ophthalmological examination that included near visual acuity using the Snellen chart, colour vision using pseudo-isochromatic plates Nos 1-8, and AG testing (white grid on black background as described by Amsler45). These examinations are the standard in screening for HCQ toxicity.67 RAG (red grid on black background) is used by some clinicians and was included in the examination.89 We also added TAG as the final component of the examination. For TAG testing, patients viewed the standard white on black AG through specialised cross polarising filters (fig 2) to reduce the perceived luminance by changing the amount of light that goes through the specialised glasses. The angle of polarisation between the two filters in the glasses was increased by 1 degree at a time until the patient stated that (s)he could no longer see the grid but could still see the white central dot. The angle was then decreased by approximately 2 degrees to increase the luminance, making the grid barely visible. Patients were asked to focus on the central white dot and report any abnormalities, which they drew on the Amsler recording chart paper (fig 3). If necessary, the polarised lenses were placed over reading glasses.

Patient demographics are shown in table 1. RA, SLE, and other connective tissue disorders affect all ethnic groups, however, the majority of our population at LA County-USC is Hispanic and this was reflected in both the control and HCQ groups equally. Most (64 of 68 or 94.1%) were women (the prevalence of RA is approximately 2.5 times, and of SLE 9–10 times higher in women than in men10) and of Hispanic ethnicity (52 of 68 or 76.5%). Patients in both groups were also essentially the same average age and range of ages. The mean age of the 68 patients was 43 years (range 21–66 years).

RESULTS

Patient visual examination data are shown in table 2. As expected, no central scotomas were detected in any patients not taking HCQ. Most of our subjects were women, therefore our findings may not be generalisable to men.

Among the 56 patients that took HCQ for at least 1 month, there was no correlation between scotoma detection and sex, ethnicity, diagnosis, HCQ dose, or length of HCQ therapy. From our analysis, when looking at high and low risk based on milligrams HCQ per kilogram patient weight, the data did not associate patients on higher doses of HCQ with an increased number of scotoma detection. In addition, as expected, there was no bias toward scotoma detection in the left or right eye. Finally, as mentioned previously, patients with known ocular disease were excluded from the study. Data collected from the patients’ ocular examinations did not reveal any abnormal findings in the baseline or annual dilated fundus examination. Humphrey 10-2 visual field testing had not been performed on any patients and baseline and follow up Amsler grid testing had been normal.

Scotomas were identified by AG in two of 56 patients taking HCQ (3.6%). In contrast, RAG identified scotomas in five of 56 patients (8.9%) and TAG identified at least one scotoma in 25 (almost 45%) of 56 patients taking HCQ. TAG testing detected both patients identified as having one or more scotoma by AG, and all five of the patients identified as having at least one scotoma by RAG. The average area of the two scotomas identified by AG were 34.5 mean square degrees per scotoma, compared to an average area of 71.2 mean square degrees per scotoma for the six detected by RAG, and 117 mean square degrees per scotoma for the 37 scotomas identified by TAG. The same five scotomas were reported to be 70 mean square degrees per scotoma when identified by RAG, and 272.4 mean square degrees when identified by TAG. Finally, TAG was more likely than RAG and AG to pick up scotomas in both eyes of a patient versus only one eye (nearly 25% more than RAG and 50% more than AG).

DISCUSSION

Previous studies have defined the diagnosis of HCQ retinopathy using two different methods. Bernstein defined it as the development of persistent paracentral or central visual field scotomas to suprathreshold white stimulus.11 According
to Easterbrook, HCQ retinopathy is defined as the presence of reproducible, bilateral field defects detected by two different visual field tests. More specifically, these tests are the Amsler grid and an automated, 10 degree visual field test. In both definitions, the finding of permanent functional visual loss is essential to the diagnosis. For the purposes of our study, a gold standard for HCQ toxicity was not defined. Our aim was to determine if there was a significant difference in relative scotoma detection using methods—AG, RAG, and TAG testing—which would be quick, easy, and reproducible in a clinical setting and at home in patients without previous ocular diagnosis related to HCQ toxicity or otherwise.

### Table 1 Patient demographics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>HCQ Dose (mg/kg/day)</th>
<th>No of months on plaquenil</th>
<th>Continuous dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>145.5</td>
<td>Other</td>
<td>F</td>
<td>AA</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>65.5</td>
<td>Other</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>69.5</td>
<td>Other</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>85.9</td>
<td>Other</td>
<td>M</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>99.5</td>
<td>Other</td>
<td>M</td>
<td>W</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>53.6</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>59.9</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>62.7</td>
<td>Other</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>40.9</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>88.6</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>56.4</td>
<td>Other</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>66.8</td>
<td>RA</td>
<td>M</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
<td>44</td>
<td>65.0</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>14</td>
<td>26</td>
<td>76.4</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>57</td>
<td>50.0</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>16</td>
<td>47</td>
<td>68.6</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>52</td>
<td>100.0</td>
<td>Other</td>
<td>M</td>
<td>W</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>18</td>
<td>48</td>
<td>72.7</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>19</td>
<td>43</td>
<td>73.6</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>20</td>
<td>48</td>
<td>69.5</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>21</td>
<td>46</td>
<td>44.5</td>
<td>SLE</td>
<td>F</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>22</td>
<td>43</td>
<td>71.4</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>23</td>
<td>64</td>
<td>45.5</td>
<td>RA</td>
<td>F</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>24</td>
<td>42</td>
<td>96.8</td>
<td>SLE</td>
<td>F</td>
<td>AA</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>25</td>
<td>46</td>
<td>62.3</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>26</td>
<td>53</td>
<td>70.9</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>27</td>
<td>62</td>
<td>87.3</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>28</td>
<td>45</td>
<td>82.7</td>
<td>Other</td>
<td>F</td>
<td>AA</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>29</td>
<td>55</td>
<td>67.7</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>30</td>
<td>59</td>
<td>60.0</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>31</td>
<td>27</td>
<td>59.1</td>
<td>SLE</td>
<td>F</td>
<td>W</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>32</td>
<td>60</td>
<td>55.5</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>33</td>
<td>35</td>
<td>64.1</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>34</td>
<td>42</td>
<td>77.3</td>
<td>SLE</td>
<td>F</td>
<td>AA</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>35</td>
<td>66</td>
<td>55.9</td>
<td>RA</td>
<td>F</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>36</td>
<td>53</td>
<td>54.5</td>
<td>RA</td>
<td>F</td>
<td>AA</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>37</td>
<td>24</td>
<td>85.9</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>38</td>
<td>24</td>
<td>66.4</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>39</td>
<td>21</td>
<td>121.4</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>40</td>
<td>34</td>
<td>59.1</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>41</td>
<td>21</td>
<td>65.5</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>42</td>
<td>41</td>
<td>65.5</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>43</td>
<td>34</td>
<td>61.4</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>44</td>
<td>32</td>
<td>75.5</td>
<td>Other</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>45</td>
<td>49</td>
<td>89.5</td>
<td>RA/SLE</td>
<td>F</td>
<td>AA</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>46</td>
<td>52</td>
<td>87.3</td>
<td>Other</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>47</td>
<td>56</td>
<td>61.8</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>48</td>
<td>34</td>
<td>60.5</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>49</td>
<td>28</td>
<td>64.1</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>50</td>
<td>27</td>
<td>74.1</td>
<td>Other</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>51</td>
<td>32</td>
<td>60.9</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>52</td>
<td>49</td>
<td>65.9</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>53</td>
<td>29</td>
<td>61.8</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>54</td>
<td>35</td>
<td>102.3</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>55</td>
<td>38</td>
<td>58.2</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>56</td>
<td>30</td>
<td>61.8</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>57</td>
<td>42</td>
<td>84.1</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>58</td>
<td>34</td>
<td>86.4</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>59</td>
<td>23</td>
<td>40.9</td>
<td>SLE</td>
<td>F</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>60</td>
<td>37</td>
<td>67.7</td>
<td>Other</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>61</td>
<td>50</td>
<td>76.4</td>
<td>SLE</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>62</td>
<td>53</td>
<td>59.5</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>63</td>
<td>52</td>
<td>54.5</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>64</td>
<td>60</td>
<td>61.8</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>65</td>
<td>53</td>
<td>68.6</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>66</td>
<td>25</td>
<td>48.2</td>
<td>Other</td>
<td>F</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>67</td>
<td>26</td>
<td>61.4</td>
<td>RA</td>
<td>F</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>68</td>
<td>48</td>
<td>61.4</td>
<td>SLE</td>
<td>F</td>
<td>AA</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; Other, connective tissue disorder not rheumatoid arthritis or systemic lupus erythematosus; RA/SLE, both rheumatoid arthritis and systemic lupus erythematosus; M, male; F, female; AA, African-American; H, Hispanic; W, white; A, Asian; N, no; Y, yes.
<table>
<thead>
<tr>
<th>Subject</th>
<th>HCQ</th>
<th>Eye</th>
<th>VA</th>
<th>Colour test plates</th>
<th>AG*</th>
<th>RAG*</th>
<th>TAG*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>RE</td>
<td>20/20</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>RE</td>
<td>20/30</td>
<td>7/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>N</td>
<td>RE</td>
<td>20/40</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>RE</td>
<td>20/25</td>
<td>7/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>N</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>N</td>
<td>RE</td>
<td>20/40</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>7/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>N</td>
<td>RE</td>
<td>20/25</td>
<td>7/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>N</td>
<td>RE</td>
<td>20/40</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>N</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>N</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Y</td>
<td>RE</td>
<td>20/20</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Y</td>
<td>RE</td>
<td>20/20</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Y</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>7/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/40</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Y</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>7/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td>140</td>
</tr>
<tr>
<td>19</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>20</td>
<td>Y</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Y</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td>78</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Y</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td>113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Y</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Y</td>
<td>RE</td>
<td>20/40</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/40</td>
<td>8/8</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Y</td>
<td>RE</td>
<td>20/25</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25</td>
<td>8/8</td>
<td>62</td>
<td>48</td>
<td>261</td>
</tr>
<tr>
<td>32</td>
<td>Y</td>
<td>RE</td>
<td>20/40</td>
<td>7/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20</td>
<td>7/8</td>
<td></td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>33</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Y</td>
<td>RE</td>
<td>20/40</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/40</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Y</td>
<td>RE</td>
<td>20/50</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Y</td>
<td>RE</td>
<td>20/20</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20</td>
<td>8/8</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Y</td>
<td>RE</td>
<td>20/20</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20</td>
<td>8/8</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Y</td>
<td>RE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Y</td>
<td>RE</td>
<td>20/40</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30</td>
<td>8/8</td>
<td></td>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>
follow up study will be necessary to determine true HCQ toxicity.

Both control patients and those with a history of HCQ therapy occasionally reported that they could not see one or more corners of the grid during AG, RAG, and/or TAG testing. Missing corners of the grid have also been reported by normal subjects. Loss of corners may not necessarily reflect pathology since the grid corners are further from the fovea and hence retinal sensitivity is decreased in that area. Therefore, these data were not considered in the analysis. One or more scotomas were identified in two patients using AG testing; five by RAG and 25 patients by TAG testing. Therefore, TAG was 12.5 times as likely to identify a patient with scotoma compared to AG and five times as likely as RAG (p = 0.003). Both patients identified as having one or more scotoma by AG were also identified by TAG and all five of the patients identified as having one or more scotomas by RAG were also identified by TAG, leading us to believe that TAG affords greater sensitivity than AG or RAG. Of the 38 scotomas detected by one or more of the three methods of testing, AG detected 5% while TAG detected 97%.

Our data demonstrated that nearly 45% of the patients taking HCQ appeared to have one or more scotomas by TAG. While 45% seems high, a high false positive rate is unlikely in that no patients in the control group were identified as having any scotomas. Retinal toxicity has been reported internationally in up to 28% of patients taking HCQ and the American Academy of Ophthalmology (AAO) recommends on HCQ screening indicate that patients may develop relative scotomas which are asymptomatic and do not show up on the fundus examination.

<table>
<thead>
<tr>
<th>Subject</th>
<th>HCQ</th>
<th>Eye</th>
<th>VA</th>
<th>Colour test plates</th>
<th>AG*</th>
<th>RAG*</th>
<th>TAG*</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>Y</td>
<td>RE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>Y</td>
<td>RE</td>
<td>20/40 8/8</td>
<td></td>
<td></td>
<td>35</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30 8/8</td>
<td>7</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Y</td>
<td>RE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td>77</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Y</td>
<td>RE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td>120</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Y</td>
<td>RE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Y</td>
<td>RE</td>
<td>20/30 7/8</td>
<td></td>
<td>100</td>
<td>385</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/40 7/8</td>
<td></td>
<td>340</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Y</td>
<td>RE</td>
<td>20/40 8/8</td>
<td></td>
<td></td>
<td>180</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30 8/8</td>
<td></td>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Y</td>
<td>RE</td>
<td>20/20 7/8</td>
<td></td>
<td></td>
<td>74</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 7/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Y</td>
<td>RE</td>
<td>20/25 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Y</td>
<td>RE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Y</td>
<td>RE</td>
<td>20/25 8/8</td>
<td></td>
<td></td>
<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25 8/8</td>
<td></td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Y</td>
<td>RE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30 8/8</td>
<td></td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Y</td>
<td>RE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30 8/8</td>
<td></td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>Y</td>
<td>RE</td>
<td>20/25 8/8</td>
<td></td>
<td></td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td>222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>Y</td>
<td>RE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td>128</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Y</td>
<td>RE</td>
<td>20/25 7/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25 7/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>Y</td>
<td>RE</td>
<td>20/25 8/8</td>
<td></td>
<td></td>
<td>70</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25 8/8</td>
<td></td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>Y</td>
<td>RE</td>
<td>20/25 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>Y</td>
<td>RE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>Y</td>
<td>RE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>Y</td>
<td>RE</td>
<td>20/40 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>Y</td>
<td>RE</td>
<td>20/25 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>Y</td>
<td>RE</td>
<td>20/25 8/8</td>
<td></td>
<td>100</td>
<td>373</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25 8/8</td>
<td></td>
<td>375</td>
<td></td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>Y</td>
<td>RE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>Y</td>
<td>RE</td>
<td>20/30 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/30 8/8</td>
<td></td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>Y</td>
<td>RE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td>120</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>67</td>
<td>Y</td>
<td>RE</td>
<td>20/20 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/20 8/8</td>
<td></td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>Y</td>
<td>RE</td>
<td>20/25 8/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>20/25 8/8</td>
<td></td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Units = square degrees of impaired visual area.
N, no; Y, yes; RE, right eye; LE, left eye; VA, visual acuity; AG, Amsler grid; RAG, red Amsler grid; TAG, Threshold Amsler grid.

Table 2 Continued
The mean area of the two scotomas identified by AG were 34.5 square degrees per scotoma, compared to 71.2 square degrees per scotoma for the six detected by RAG, and 117 square degrees per scotoma for the 37 scotomas identified by TAG. TAG identified an affected area more than three times the area of that identified by AG. Of the five scotomas detected by both RAG and TAG, TAG detected an average area per scotoma nearly four times that of RAG (p = 0.02). TAG tests the central visual field at threshold and is able to detect a larger affected area of the same scotoma because it includes relative scotomas of lesser severity.

It seems most reasonable to assume that an appropriate screening test would detect scotomas bilaterally. In our study, AG never detected the involvement of both eyes while RAG only detected it 20% of the time. TAG identified one or more scotomas in both eyes at least 52% of the time.

One individual, patient 63, had been on HCQ treatment for only 1 month but had the largest bilateral scotomas in terms of area of any patient in our study. She had never taken HCO previously and did not have a history of ocular pathology, but had missed her appointment for a baseline ophthalmological examination. It is highly unlikely that the TAG results were secondary to HCQ toxicity, therefore, this case highlights the need to obtain both a baseline and an early examination in patients who are starting HCQ treatment.

TAG is an easy to perform, quick, and high yield alternative to detect shallow/relative scotomas reflecting areas of depressed retinal activity secondary to HCQ toxicity. These scotomas may go undetected early on with AG or RAG testing and lead to irreversible visual changes. TAG offers clinicians a novel alternative for the detection of central visual field defects in patients receiving HCQ therapy. TAG can also be used as a quantitative method to monitor the progression of macular changes in these patients.

If retinal toxicity is diagnosed, the HCQ is usually immediately discontinued as this may lead to clinical improvement.19 Reversibility of visual loss diminishes with time, therefore, early detection is important.15-17 Some of the retinal changes seen in our patient population may be reversible functional changes. Because no gold standard for toxicity was defined, and because HCQ therapy is such an important component of treatment in many patients with connective tissue disorders, our study cannot be used to determine when HCQ therapy should be stopped. None the less, while controversy does exist in the literature regarding the validity and sensitivity of AG and TAG testing, the results from our study show significant findings with TAG testing that may be indicative of permanent retinal toxicity.18-19 Long term follow up of HCQ patients with many retinal measures will help to determine if the scotomas have enlarged or changed and when the point of irreversibility is crossed. In the meantime, prudentice requires careful monitoring by the most sensitive measures including TAG.

In recognition of the great benefit that HCQ brings to patients with rheumatoid arthritis and other connective tissue disorders, we recommend careful monitoring and only consideration of drug cessation with progression of TAG scotomas or demonstration of classic ophthalmological impairments. Owing to the serious nature of the retinal toxicity that can be caused by HCQ, even after cessation of the drug, TAG can be used as an effective screening method to detect these scotomas before permanent damage ensues.

ACKNOWLEDGEMENTS
We are grateful to Robert A Almony, III, Lori Levin, Michael Payle, Michelle Ris, Toufan Rahimpour, Anne Rosenfeld, Fred Ross-Cisneros, and NIH EY03040.

Authors' affiliations
A Almony, S Garg, A A Sadun, Doheny Eye Institute, Los Angeles, CA, USA
R K Peters, R Mamet, Department of Preventive Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA
J Tsong, Department of Ophthalmology, George Washington University Medical Center, Washington, DC, USA
B Shibuya, R Kilioud, Department of Rheumatology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

REFERENCES
Long term outcome of trichiasis surgery in the Gambia


Background: Trichiasis surgery is believed to reduce the risk of losing vision from trachoma. There are limited data on the long term outcome of surgery and its effect on vision and corneal opacification. Similarly, the determinants of failure are not well understood.

Methods: A cohort of people in the Gambia who had undergone surgery for trachomatous trichiasis 3–4 years earlier was re-assessed. They were examined clinically and the conjunctiva was sampled for Chlamydia trachomatis polymerase chain reaction (PCR) and general bacterial culture.

Results: In total, 141/162 people were re-examined. Recurrent trichiasis was found in 89 (55.8%) operated eyes and 52 (24.3%) eyes had five or more lashes touching the globe. Corneal opacification improved in 36 of 78 previously affected eyes. There was a general deterioration in visual acuity between surgery and follow up, which was greater if new corneal opacification developed or trichiasis returned. Recurrent trichiasis was associated with severe conjunctival inflammation and bacterial infection. C trachomatis was detected in only one individual.

Conclusions: Recurrent trichiasis following surgery is a common potentially sight threatening problem. Some improvement in the cornea can occur following surgery and the rate of visual loss tended to be less in those without recurrent trichiasis. The role of conjunctival inflammation and bacterial infection needs to be investigated further. Follow up of patients is advised to identify individuals needing additional surgical treatment.

Trachoma is the leading infectious cause of blindness worldwide. Recurrent episodes of Chlamydia trachomatis infection promote a chronic follicular conjunctivitis, which can lead to progressive conjunctival scarring, trichiasis, entropion, and ultimately blinding corneal opacification. The World Health Organization (WHO) currently estimates that 1.9 million people are blind from trachoma and a further 7.6 million have trichiasis requiring lid surgery (provisional estimates presented to the IAPB Task Force Meeting, India, 2003). In a collaborative effort to control blindness trachoma by the year 2020 the WHO and its partners are implementing environmental improvement to interrupt transmission. 1 Of these interventions only trichiasis surgery has been demonstrated to reduce visual loss, largely because of the slowly progressive nature of the disease.2

In many endemic countries minor trichiasis (<5 lashes touching the globe) is often managed by repeated epilation. Major trichiasis (5+ lashes touching the globe) is usually treated surgically. Several alternative procedures are in use. In a formal comparison of a number of these the bilamellar tarsal rotation (BLTR) had the lowest recurrence rate of approximately 20% at 1 year and is therefore recommended by the WHO. 2 3 In the Gambia and many other endemic countries the posterior lamellar tarsal rotation (PLTR) is used. This is believed to produce results comparable to the BLTR. 4 5 Despite this reported short term success there is concern that the long term results of surgery are less favourable. 6 7

A number of factors may influence whether trichiasis returns following surgery: type of operation, quality of surgery, severity of disease, individual wound healing responses, infection with C trachomatis and other bacteria. The progression of corneal opacification (CO) may be promoted by a range of factors in addition to trichiasis such as bacterial infection and ocular dryness. A greater understanding of these processes could aid the development of interventions, which might limit the recurrence of trichiasis and the loss of sight following surgery.

There is currently limited long term prospective data on recurrent trichiasis and changes in CO and vision following surgery. This is in part because preoperative clinical data are not usually available. In 1998 studies were conducted in the Gambia during which individuals underwent PLTR surgery for trichiasis. 8 9 Detailed preoperative assessment data and contact information were available. Therefore, this group offered an opportunity to assess the outcome of surgery at 3–4 years and to examine some of the potential determinants of recurrent trichiasis.

METHODS

Ethical permission

This study was approved by the Gambian Government/Medical Research Council joint ethics committee and is in accordance with the tenets of the Declaration of Helsinki.

Clinical assessment

Individuals who had undergone trichiasis surgery in 1998 during the course of previously described studies were revisited at their homes 3–4 years later. 8 9 Preoperative clinical data were available for these patients including Tumbling-E Snellen visual acuity at 6 metres, severity of trichiasis (major or minor) and the presence or absence of CO overlying the pupil. Trained ophthalmic nurses using the PLTR procedure had performed the surgery.

At follow up the visual acuity was measured using a Tumbling-E reduced logMAR chart at 4 metres or 1 metre. 10 If the subject was unable to read the largest letters at 1 metre the vision was graded as counting fingers, hand movements,
perception of light, or no perception of light. Patients were examined using 2.5× binocular loupes and a bright torch. The clinical signs were graded according to the WHO trachoma grading system. The number of eyelashes touching the cornea and other parts of the eye when in primary position were counted and lid closure defects measured. Corneal opacification was considered to be visually significant if it obscured at least part of the pupil margin (CC2/CC3 or CO). Conjunctival inflammation was considered significant if there were prominent papillae and haziness of the tarsal blood vessel (P2 or P3).

The conjunctiva was anaesthetised with proxymetacaine 0.5% eye drops (Minims, Chauvin Pharmaceuticals, Romford, UK). A conjunctival swab sample (Dacron polyester tipped swab: Hardwood Products Company, Guilford, ME, USA) was collected from the inferior fornix and immediately placed into a sterile tube containing STGG broth (skimmed milk-tryptone-glycerol-glucose broth) for bacterial culture. A second swab sample for C trachomatis PCR was collected from the upper tarsal conjunctiva and placed in a dry tube. Both sets of samples were kept on ice before transfer to −70°C or −20°C freezers, respectively, later the same day. Individuals with trichiasis were offered further surgery under local anaesthetic and patients’ homes (12.2%).

RESULTS

Patient characteristics

In total, 141/162 (87.0%) individuals who had undergone trichiasis surgery in 1998 were re-assessed. Of the 21 who were not seen 14 had died, two refused, and five were untraceable. They came from the Western, North Bank and Lower River Divisions of the Gambia. The patients were predominantly female (74.5%), had a median age of 60 years (interquartile range 50–70 years), and were mostly of the Mandinka ethnic group (80.1%). The median time from surgery to re-assessment was 3.5 years (interquartile range: 3.2–4.4 years; total range 2.9–4.5 years). In all, 214 eyes had undergone surgery; 20 had bilateral surgery and patients’ homes (12.2%).

Recurrent trichiasis

At follow up 89/214 (41.6%) previously operated eyes had some degree of trichiasis and 52/214 (24.3%) had five or more lashes touching the eye, including those with extensive epilation. The severity of trichiasis at follow up is presented in table 1. The recurrence rate was the same for both left and right eyes (right 41.4%, left 41.8%). Of the 73 individuals who had undergone bilateral surgery 20 had unilateral recurrence and another 20 had bilateral recurrence.

Table 2 Changes in clinically significant corneal opacification (CO), before and after trichiasis surgery

<table>
<thead>
<tr>
<th>CO before surgery</th>
<th>CO after surgery</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>52</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>36</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>103</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>139</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>191</td>
</tr>
</tbody>
</table>

The clinical signs were graded according to the WHO trachoma grading system. The number of eyelashes touching the eye, including those with extensive epilation. The severity of trichiasis at follow up is presented in table 1. The recurrence rate was the same for both left and right eyes (right 41.4%, left 41.8%). Of the 73 individuals who had undergone bilateral surgery 20 had unilateral recurrence and another 20 had bilateral recurrence.

Corneal opacification

Preoperative and postoperative corneal grading data was available on 191 eyes (table 2). Before surgery, 78/191 (40.8%) eyes had clinically significant CO, while at follow up 52/191 (27.2%) had CO. This represents a significant reduction in the amount of CO following surgery: OR: 0.28, 95% CI: 0.12 to 0.57, p<0.001 (McNemar’s χ² test). New opacification developed in 10 eyes, of which six had recurrent trichiasis. CO resolved in 36/78 eyes (46.2%). Of these 36 eyes, 17 had recurrent trichiasis. Of the 42 eyes that had CO on both occasions, 20 had recurrent trichiasis. The postoperative trichiasis tended to be less severe in eyes that had resolved CO compared with those with CO on both occasions (mean: three lashes vs eight lashes, respectively). Corneal opacification at follow up was more commonly found in eyes with lashes touching the cornea (23/63: 36.5%) compared to eyes with lashes only touching bulbar conjunctiva (2/16: 12.5%), however, this did not reach statistical significance. Corneal opacification in eyes with recurrent trichiasis was less common if extensive epilation was practised (2/14;
14.3%) compared to eyes that were not epilated (25/73; 34.3%), again this difference was not significant.

**Visual acuity**

Visual acuity data were available for 199 eyes before and after surgery. Excluding eyes that had a visual acuity of counting fingers or less on either occasion, there was a mean deterioration in vision of 0.16 logMAR units, which was statistically significant (p < 0.0001, paired, two-sided t-test). The reduction in visual acuity tended to be less among those without recurrent trichiasis (0.13 logMAR) compared to those with recurrent trichiasis (0.22 logMAR); however, these groups were not statistically different (p = 0.124). When eyes with a visual acuity of counting fingers or less are included the mean deterioration was 0.21 logMAR units (p < 0.0001, paired, two-sided t-test). There was no difference in the reduction of vision between those with or without trichiasis at follow up. Visual acuity deteriorated more rapidly in eyes that developed new CO compared with those that did not (0.54 ± 0.06 logMAR, respectively. p = 0.003, paired, two-sided t-test). There was a non-significant trend towards less rapid visual loss in eyes in which the CO resolved compared with those in which it persisted (0.15 ± 0.46 logMAR, respectively. p = 0.18, paired, two-sided t-test).

**Conjunctival infection**

*C trachomatis* PCR testing was conducted on conjunctival swab samples from 135 of the 141 study participants. Only one gave a positive test result. Bacterial culture samples were collected from 155/214 operated eyes. Pathological isolates were grown from 42/155 (27.1%) samples. The isolation rate was higher in eyes with recurrent trichiasis (27/68; 39.7%) compared to those without recurrent trichiasis (15/87; 17.2%). *Streptococcus pneumoniae* and *Staphylococcus aureus* were the most frequently cultured organisms (table 3). Eyes with trichiasis were more frequently infected with *S pneumoniae* than those without trichiasis (22.1% vs 3.4%, respectively. OR: 7.92, 95% CI: 2.19 to 28.7, p = 0.002).

**Risk factors for recurrent trichiasis**

Univariate associations between various risk factors and any trichiasis at follow up are presented in table 4. There was a tendency to more frequent recurrence in older age groups. Bacterial infection and conjunctival inflammation (grade P2 or P3) were both associated with recurrent trichiasis. Multivariable logistic regression models for recurrent trichiasis were developed, which was adjusted for the correlation between eyes in the case of bilateral surgery by generalised estimating equations (table 5). These indicated significant associations between recurrent trichiasis and conjunctival inflammation and bacterial infection.

**DISCUSSION**

Surgery for trachomatous trichiasis is believed to reduce the risk of blindness. There is, however, limited information on the long term outcome of this intervention, the determinants of recurrent trichiasis, its effect on vision and CO. In this study a group of subjects, in whom preoperative clinical data were available, was re-examined 3.5 years after trichiasis surgery.

Recurrent trichiasis was common (41.6%). The finding that 24.3% of operated eyes had major trichiasis at 3.5 years is of particular concern, as such eyes are probably at high risk of progressive corneal damage. These trichiasis recurrence rates are comparable to previously reported 3 year outcomes from trachoma control programmes, which have ranged up to 62%. Recurrence rates reported by more formal prospective clinical studies have tended to be lower at around 20% after 2 years. In one of these only 3.5% of eyes had three or more lashes touching the eye at 3 years. These studies have tended to use one or just a few highly trained individuals to perform the surgery, and therefore may not reflect the usual situation in trachoma control programmes.

### Table 3 Pathological conjunctival bacterial isolates

<table>
<thead>
<tr>
<th>Organism</th>
<th>All eyes</th>
<th>No trichiasis</th>
<th>Trichiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td><em>S pneumoniae</em></td>
<td>18</td>
<td>42.9</td>
<td>3</td>
</tr>
<tr>
<td><em>Streptococcus group C</em></td>
<td>6</td>
<td>14.3</td>
<td>1</td>
</tr>
<tr>
<td><em>Staphylococcus spp</em></td>
<td>3</td>
<td>7.1</td>
<td>1</td>
</tr>
<tr>
<td><em>S viridans</em></td>
<td>1</td>
<td>2.4</td>
<td>1</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>13</td>
<td>30.9</td>
<td>8</td>
</tr>
<tr>
<td><em>Coliform spp</em></td>
<td>1</td>
<td>2.4</td>
<td>1</td>
</tr>
<tr>
<td>Number of isolates</td>
<td>42</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Number of eyes sampled</td>
<td>155</td>
<td></td>
<td>87</td>
</tr>
</tbody>
</table>

### Table 4 Univariate associations between recurrent trichiasis and various factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>50–59</td>
<td>1.64</td>
<td>0.69 to 3.91</td>
<td>0.263</td>
</tr>
<tr>
<td>60–69</td>
<td>1.23</td>
<td>0.56 to 2.72</td>
<td>0.609</td>
</tr>
<tr>
<td>70+</td>
<td>2.23</td>
<td>1.08 to 5.02</td>
<td>0.031</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.67</td>
<td>0.36 to 1.27</td>
<td>0.219</td>
</tr>
<tr>
<td>Ethnic group (non-Mandinka)</td>
<td>0.59</td>
<td>0.29 to 1.22</td>
<td>0.156</td>
</tr>
<tr>
<td>Surgery in hospital</td>
<td>1.01</td>
<td>0.58 to 1.75</td>
<td>0.985</td>
</tr>
<tr>
<td>Eye (right)</td>
<td>1.01</td>
<td>0.59 to 1.74</td>
<td>0.964</td>
</tr>
<tr>
<td><em>C trachomatis</em> infection</td>
<td>0.82</td>
<td>0.42 to 1.61</td>
<td>0.575</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>3.16</td>
<td>1.51 to 6.62</td>
<td>0.002</td>
</tr>
<tr>
<td>Conjunctival inflammation</td>
<td>4.01</td>
<td>1.49 to 10.8</td>
<td>0.006</td>
</tr>
</tbody>
</table>
To our knowledge this is the first study to evaluate the impact of trichiasis surgery on CO. Encouragingly, surgical correction of trichiasis was followed by a reduction in the prevalence of CO, even if some trichiasis returned. This suggests that by reducing the burden of trichiasis a degree of corneal recovery can occur. The majority of eyes developing new opacification had recurrent trichiasis; however, a few developed CO in the absence of recurrent trichiasis. This suggests that other factors contribute to corneal damage such as ocular infection or dryness, and warrant detailed investigation. It is possible that some of the changes in the grade of CO could be due to misclassification. Different observers performed baseline and follow up examinations. Corneal opacification is considered to be significant when it overlies any portion of the pupil; however, this could be a bit variable depending on ambient light levels.

There was a general deterioration in visual acuity between surgery and follow up. This may in part be due to other age related changes such as cataract. There was a non-significant trend towards a greater deterioration in vision if the trichiasis returned. In the absence of a randomly assigned non-operated control group it is not known how much deterioration would have occurred without surgery. There was, however, a significantly greater deterioration in vision in those who developed new corneal opacification. Short term improvements in vision have previously been reported following trichiasis surgery. 7 8

Recurrent trichiasis was associated with conjunctival inflammation. This clinical appearance is relatively common in individuals with trichiasis. It may reflect an ongoing pathological inflammatory process, which could contribute to progressive scarring and recurrent trichiasis. 7 The grading of conjunctival inflammation in a heavily scarred individual can sometimes be difficult as there is limited epithelium to develop a papillary response and the scarring may obscure the tarsal vessels. A study of conjunctival biopsies collected during trichiasis surgery found that a proportion had an inflammatory cell infiltrate, which corresponded to clinical inflammation. 24 A number of factors could provoke the inflammation including mechanical irritation from inturned lashes, chlamydial or bacterial infection, or a primary immune mediated process. Although conjunctival inflammation in people living in a trachoma endemic region might be expected to be due to infection with C trachomatis, in this group of patients this is unlikely as only one individual had detectable chlamydial DNA by PCR. This is in contrast with a small study from Nepal, which found an association between recurrent trichiasis and chlamydial detection by PCR. 25

Bacterial infection was independently associated with recurrent trichiasis following surgery. This is to our knowledge the first time this has been observed. Previously, an association was found in a subgroup of this cohort between bacterial infection and progression of CO before surgery. 26 A similar spectrum of organisms was isolated. It is likely that eyes with trichiasis are more vulnerable to bacterial infection. Conversely, although a role for bacteria in the pathogenesis of blinding trachoma has been suggested for many years, it still remains poorly defined. 26 It is biologically plausible that persistent bacterial conjunctivitis could contribute to progressive cicatricial changes through chronic inflammation.

Our study has a number of potential limitations, which should be borne in mind. Firstly, the preoperative assessment was by a different observer from the follow up and it was not possible to assess potential interobserver variability. However, the principal clinical outcome measures used in this study, presence of trichiasis and corneal opacification, are relatively objective, clearly defined, and have been shown to have good interobserver reliability. 27 Secondly, a Snellen visual acuity was measured before surgery and converted to a logMAR equivalent for comparison with the follow up measurement. This may have introduced some systematic bias in the comparison. Finally, it is not known exactly when the trichiasis returned in this group of patients. Recurrence in the early postoperative period may arise for different reasons than late recurrence, such as limitations of the surgical method, inter-surgeon variability, and differences in wound healing responses.

This study indicates that recurrent trichiasis is a common problem, which represents a significant threat to the sight of many. It needs to be considered by trachoma control programmes as they plan surgical services. Wherever possible trichiasis patients should be re-examined on an ongoing basis following surgery to identify those in need of additional treatment. On a more encouraging note this study has demonstrated that some restoration of the cornea can occur after surgery and that this is associated with a slowing of the rate of visual loss. There is a pressing need to find ways to improve the long term outcome of surgery. This may involve further randomised controlled trials to optimise the surgical technique, clinical audit to monitor surgeon specific outcomes, and interventions to control infection. In addition, the part of other factors besides trichiasis in the pathogenesis of CO needs to be examined as correcting trichiasis alone may not be sufficient to prevent trachoma related blindness in all cases.

ACKNOWLEDGEMENTS

The authors would like to thank the ophthalmic nurses of the Gambian National Eye Care Programme and the field staff from the Medical Research Council Laboratories for their hard work often under quite challenging conditions.

Authors’ affiliations

M J Burton, R J C Bowman, N D E Alexander, D C W Mabey, A Foster, G J Johnson, R L Bailey, International Centre for Eye Health, London School of Hygiene and Tropical Medicine, London, UK

www.bjophthalmol.com

<table>
<thead>
<tr>
<th>Variable</th>
<th>1+ Lashes</th>
<th>95% CI</th>
<th>p Value</th>
<th>5+ Lashes</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>1.00</td>
<td>0.35 to 2.84</td>
<td>0.997</td>
<td>1.48</td>
<td>0.45 to 4.88</td>
<td>0.521</td>
</tr>
<tr>
<td>50–59</td>
<td>1.19</td>
<td>0.42 to 3.41</td>
<td>0.736</td>
<td>1.37</td>
<td>0.41 to 4.50</td>
<td>0.607</td>
</tr>
<tr>
<td>60–69</td>
<td>1.00</td>
<td>0.35 to 2.84</td>
<td>0.997</td>
<td>1.48</td>
<td>0.45 to 4.88</td>
<td>0.521</td>
</tr>
<tr>
<td>70+</td>
<td>1.44</td>
<td>0.57 to 3.64</td>
<td>0.434</td>
<td>2.14</td>
<td>0.74 to 6.18</td>
<td>0.128</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.63</td>
<td>0.28 to 1.43</td>
<td>0.267</td>
<td>0.45</td>
<td>0.19 to 1.04</td>
<td>0.064</td>
</tr>
<tr>
<td>Conjunctival inflammation</td>
<td>2.06</td>
<td>1.03 to 4.12</td>
<td>0.040</td>
<td>2.85</td>
<td>1.33 to 6.14</td>
<td>0.007</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>2.51</td>
<td>1.04 to 6.07</td>
<td>0.041</td>
<td>2.42</td>
<td>1.08 to 5.42</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Table 5  Multivariable logistic regression models for associations between recurrent trichiasis and various factors, adjusting for the correlation between eyes in bilateral cases by generalised estimating equations.
Outcome of trichiasis surgery

M J Burton, E A N Aryee, U N Irumapayi, R A Adebola, L Bailey, Medical Research Council Laboratories, Fajara, the Gambia
R J C Bowman, H Faal, National Eye Care Programme, the Gambia
R J C Bowman, CCBRT Disability Hospital, Dar Es Salaam, Tanzania
S K West, Dana Centre for Preventive Ophthalmology, Johns Hopkins University, Baltimore, MD, USA
G J Johnson, Division of Epidemiology and International Eye Health, Institute of Ophthalmology, London, UK

Sponsorship: This study was supported by a grant from the Wellcome Trust.
Competing interests: none declared
Ethical approval: This study was approved by the Gambian Government/Medical Research Council Joint Ethics Committee.

REFERENCES
Corneal sensation after myopic and hyperopic LASIK: clinical and confocal microscopic study

M A Bragheeth, H S Dua

Aim: To assess the long term (1 year) effect of myopic and hyperopic LASIK on corneal sensation and innervation.

Methods: 83 eyes of 43 patients having LASIK were evaluated. According to the preoperative spherical equivalent, the eyes were divided into three groups: group 1, myopia from $-0.75$ to $-6.00$ D; group 2, myopia from $-6.25$ to $-11.50$ D; and group 3, hyperopia from $1.25$ to $5.00$ D. Corneal sensation was measured and in vivo confocal microscopy (IVCM) was done at the central cornea before, and at 1 month, 3 months, 6 months, and 1 year after LASIK.

Results: The mean corneal sensation in group 1 was greater than in groups 2 and 3 at all postoperative measurements. The difference between group 1 on one hand and groups 2 and 3 on the other hand was statistically significant at 1 month and 3 months after LASIK and was not statistically significant afterwards. IVCM study of 27 eyes revealed that the number and length of nerve fibre bundles in the sub-basal region decreased after LASIK and was significantly lower at all times after surgery despite the return of corneal sensation to preoperative level.

Conclusion: After LASIK, central corneal sensitivity is decreased for as long as 6 months or more. The results suggest that lamellar cutting of the cornea during LASIK impairs corneal sensitivity and is related to the ablation depth. The diameter of ablation too may contribute to this drop in sensitivity. The return of corneal sensations does not directly correlate with the regeneration of nerve fibres as determined by confocal imaging. Sensations return to normal values before complete restoration of normal innervation if this indeed ever occurs.

The sensory innervation of the cornea is derived from the ophthalmic and maxillary branches of the trigeminal nerve. These nerve fibres are myelinated until they penetrate the limbus and form thick nerve bundles surrounded by the Schwann cells in the anterior third of the stroma. In human cornea these bundles divide dichotomously or trichotomously, bend 90 degrees, lose their Schwann cell sheath, and penetrate Bowman’s layer. Then they bend again almost at right angles forming the basal epithelial/subepithelial nerve plexus between the basal epithelial cells and Bowman’s layer. Fibres of this plexus branch both horizontally and vertically sending nerve terminals between the epithelial cells. There are three classes of these corneal sensory receptors—mechanoreceptors, polymodal receptors, and thermoreceptors—that are responsible for mechanical, chemical, and thermal sensation, respectively. A-δ fibres react to mechanical sensation and the C fibres to temperature. Some of the stromal keratocytes are innervated by stromal nerve fibres and both basal and wing cells have been supposed to be directly innervated by epithelial nerve fibres.

Normal corneal sensitivity is essential to normal corneal structure and function. Touching the cornea triggers one of the most sensitive protective reflexes of the human body. The threshold of sensitivity, especially in the centre of the cornea, is exceedingly low, so pathological changes can be diagnosed early and precisely and corneal sensation can be used for diagnosis, follow up, and even for prognosis of various corneal disorders.

Loss of normal corneal sensation may compromise the protective blink reflex, delay epithelial wound healing, decrease tear flow, and be associated with neurotrophic keratitis, sterile corneal melts, and infectious keratitis.

Cochet and Bonnet have shown that sensitivity of the cornea is greatest at its centre and decreases towards the periphery. The upper part of the cornea is the least sensitive, and the temporal part is highly sensitive.

During laser in situ keratomileusis (LASIK) surgery the superficial stromal nerves are cut in the flap margin and the nerves in the stromal bed under the flap are subsequently exposed to excimer laser photoablation. The LASIK flap is usually 160 µm thick and the additional ablation depth of the excimer laser varies according to the desired myopic correction. Both factors (flap cutting and laser ablation) contribute to the innervation damage, which develops following LASIK surgery.

We undertook a prospective study to assess the effect of myopic and hyperopic LASIK on corneal sensation and corneal innervation.

PATIENTS AND METHODS
In a prospective, comparative, non-randomised consecutive case study, 83 eyes of 43 patients, 11 male and 32 female, with a mean age of 31.2 years (range 23–40 years) underwent LASIK. Surgeries were performed by the same surgeon (HSD) from August 2001 to December 2002. According to the preoperative spherical equivalent, the eyes were divided into three groups: group 1, myopia from $-0.75$ to $-6.00$ D; group 2, myopia from $-6.25$ to $-11.50$ D; and group 3, hyperopia from $1.25$ to $5.00$ D (table 1). All eyes had normal corneal sensation before LASIK (see table 2).

Abbreviations: BSCVA, best spectacle corrected visual acuity; IVCM, in vivo confocal microscopy; LASIK, laser in situ keratomileusis; NFBs, nerve fibre bundles; UCVA, uncorrected visual acuity
Preoperative examinations included personal medical ocular history, uncorrected visual acuity (UCVA), best spectacle corrected visual acuity (BSCVA), corneal topography (with the Eye Sys system 2000, Eye Sys Technologies, Houston, TX, USA), ultrasonic pachymetry (Advent Pachymeter; Mentor), manifest refraction, tonometry, slit lamp microscopy, corneal sensitivity testing (using the Cochet–Bonnet aesthesiometer; Luneau, Paris, France), and dilated fundus examination. Pupil size was measured with the Infrared Pupilscan II (Keeler, Broomall, PA, USA) in a mesopic room environment. In vivo confocal microscopy (IVCM) was done for 27 eyes (10 eyes from group 1, 10 eyes from group 2, and seven eyes from group 3). Patients recruited for IVCM were age and sex matched. Informed consent was obtained from all patients after they received a detailed description of the surgical procedure and its known risks, and if they wore contact lenses they had been advised to discontinue soft lens wear for 2 weeks or hard contact lens wear for 1 month.

The standard LASIK technique was used for all patients. Treatment was done under topical anaesthesia using 1% amethocaine hydrochloride eye drops (Minims; Chauvin, Romford, UK). A drop of 2.5% hydroxypropyl methylcellulose eye drops (Goniosol; Ciba Vision) was placed on the tip of the objective lens as an optical coupling medium, and the lens was manually advanced until the medium contacted the surface of the central cornea. A full thickness scan, consisting of a series of confocal images, was recorded as the focal plane was advanced from anterior to the epithelium to posterior to the endothelium. Real time images were captured using a low light level video camera and the images were recorded on an S-VHS videotape (Fuji Magnetics, Kleve, Germany) using a video cassette recorder. Digital images were stored on a computer workstation (PC Pentium, Tomey Base, Confo Scan P4, Tomey) at 25 frames/s. Each image represented a coronal video cassette. Digital images were stored on a computer workstation (PC Pentium, Tomey Base, Confo Scan P4, Tomey) at 25 frames/s. Each image represented a coronal scan of the central cornea. Clear digital images were selected by the same investigator, for all patients for all visits, for further analysis.

Nerve fibre bundles (NFBs) appeared as bright, well defined, linear structures that were sometimes branched and usually appeared in several consecutive frames. All confocal scan images of sufficient quality for sub-basal nerves visualisation were evaluated for each patient. The NFBs per scan in two to four scans per eye per visit was determined and measured in the sub-basal region and in the stromal flap (layer between the most anterior keratocyte and the flap interface). Based on the confocal images, the sub-basal NFBs were grouped into four different categories based on their morphology: (1) no nerve images, (2) only short (<200 μm) NFBs, (3) long (≥200 μm) NFBs without interconnections, and (4) long NFBs with interconnections (see fig 2).

Statistical analysis was performed using Excel (Microsoft, Inc) and SPSS for Windows v11.0.1. Results are presented as means (SD) and were compared with the Student’s two tailed t test for unpaired samples. Mann Whitney test, a
non-parametric test, was used to analyse the data that are not normally distributed. Median numbers of long sub-basal NFBs were related to corneal sensation in each group at each follow up visit by using the Friedman test, a non-parametric version of the repeated measures analysis of variance. A p value of less than 0.05 was considered statistically significant.

RESULTS

Mean preoperative and postoperative central corneal sensations of all groups are shown in table 2, and in figure 1.

The preoperative mean corneal sensation was 57.93 (4.47) mm, 56.25 (10.62) mm, and 58.00 (2.58) mm at the central cornea in groups 1, 2, and 3 respectively. These baseline preoperative corneal sensation differences between the three groups were not statistically significant (p > 0.05).

One month after LASIK, the mean corneal sensation in group 1 (39.86 (10.17) mm) was greater than in groups 2 and 3 (29.50 (17.24) mm and 29.00 (14.87) mm, respectively). The difference was statistically significant (p < 0.05).

Three months after LASIK, the mean corneal sensation in group 1 (45.71 (08.99) mm) was greater than in the other groups 2 and 3 (37.69 (13.17) mm and 36.00 (11.25) mm, respectively). The difference was statistically significant (p = 0.01).

The difference between the mean preoperative corneal sensation and the mean corneal sensation 1 year after LASIK treatment was not statistically significant in the three groups (p > 0.05).

Slit lamp microscopy and fluorescein staining revealed evidence of superficial punctate keratitis (SPK) in 13 (15.6%) eyes at 1 month post-LASIK (four from group 1, six from group 2, and three from group 3). At 3 months post-LASIK, the number of eyes that had SPK were eight eyes (9.6%) (two, four, and two in the three groups, respectively) and at 6 months post-LASIK only four eyes (4.8%) showed SPK (one, two, and one in the three groups respectively).

IVCM study of 27 eyes, before and after LASIK, revealed that the number and length of NFBs in the sub-basal region decreased after LASIK (table 3) and was significantly lower at all times after surgery than it was before surgery (p < 0.001). It increased 6 and 12 months after LASIK, but remained less than the preoperative value. The number and length of the sub-basal NFBs (fig 2), was lower in groups 2 and 3 (high myopia and hyperopia groups) than in group 1 (mild to moderate myopia).

In the flap stroma, the stromal NFBs appeared as thick lines that could be seen through several successive optical sections. The number and length of NFBs after surgery were also less than before LASIK but we could not quantify them because of their small number and inconsistency of their detection. We could not also study them statistically for the possible difference and correlation to the LASIK treatment.

DISCUSSION

The cornea is the most richly innervated surface tissue of the body. Interest in the sensitivity of the cornea dates back to the 19th century. The German physiologist Von Frey in 1894, concluded that pain was the only sensation perceived by the cornea.

Before describing the changes in corneal sensation after LASIK, it is important to be aware of the following normal physiological variations in corneal sensitivity. Corneal sensitivity varies with eccentricity; the cornea is most sensitive at its centre and sensitivity decreases gradually towards the periphery. This shows a good correlation with the distribution of the sensory nerve terminals. A diurnal variation in corneal sensitivity has been noted; the sensitivity is highest in the evening and lowest in the morning, a trend that seems to be related to corneal hypoxia during sleep. Diurnal variation is an important consideration in longitudinal studies where repeated measurements are taken over time. Corneal sensitivity appears to vary little over the first four decades of life but later it shows a gradual decline (hypoesthesia). Sex differences also require consideration as the hormonal changes which occur during the menstrual cycle and pregnancy may be associated with changes in corneal sensitivity.

During LASIK surgery the superficial stromal nerves are cut in the flap margin and the nerves in the stromal bed under the flap are subsequently exposed to excimer laser photoablation.

![Figure 1](https://www.bjophthalmol.com)

**Figure 1** Graph showing the mean corneal sensitivity as measured in millimetres with the Cochet-Bonnet aesthesiometer (y axis) over the follow up period of 1 year (x axis). Group 1 (low myopes) shows a significant difference compared to the other two groups (high myopes and hyperopes). By 1 year all three groups were similar but had not recovered to preoperative levels.

![Table 2](https://www.bjophthalmol.com)

**Table 2** Mean corneal sensation (SD) before and after LASIK shown as millimetres of Cochet-Bonnet filament length at each time point for each of the three groups examined.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative*</td>
<td>57.93 (4.47) mm</td>
<td>56.25 (10.62) mm</td>
<td>58.00 (2.58) mm</td>
<td>0.43</td>
</tr>
<tr>
<td>1 month postop</td>
<td>39.86 (10.17) mm</td>
<td>29.50 (17.24) mm</td>
<td>29.00 (14.87) mm</td>
<td>0.01</td>
</tr>
<tr>
<td>3 months postop</td>
<td>45.71 (08.99) mm</td>
<td>37.69 (13.17) mm</td>
<td>36.00 (11.25) mm</td>
<td>0.02</td>
</tr>
<tr>
<td>6 months postop</td>
<td>48.01 (09.76) mm</td>
<td>47.08 (11.75) mm</td>
<td>45.65 (07.75) mm</td>
<td>0.09</td>
</tr>
<tr>
<td>1 year postop</td>
<td>52.25 (06.17) mm</td>
<td>51.00 (07.07) mm</td>
<td>51.87 (08.84) mm</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*8, 6, and 4 eyes in groups 1, 2, and 3 respectively wore contact lenses preoperatively. The average corneal sensation as measured by Cochet-Bonnet aesthesiometer for these patients was 56.87 mm, 55.83 mm, and 58.75 mm. There was no statistical difference in preoperative corneal sensation between contact lens wearers and that of the rest of the group.
The nerves distal to a surgically induced corneal wound degenerate, thereafter the proximal trunks begin to send regenerating nerve fibres into the wounded area.12

A potentially important feature of LASIK is that it spares the epithelium, the Bowman layer, a considerable proportion of the anterior stromal nerve plexus and the corneal nerves in the hinge region, which remain unaffected. Furthermore, the flap contains an undisturbed Bowman’s layer and the original Schwann cell pathways, which might facilitate the process of nerve recovery.

Aesthesiometry is a reproducibly accurate measure of corneal sensation. The most popular device for this purpose is the Cochet-Bonnet aesthesiometer (Luneau), which consists of a calibrated nylon filament for mechanical stimulation.13 It has limitations in its sensitivity as a test but is the most practical method available. The conclusions of this study should be interpreted within the limits of this method of evaluation.

Corneal sensation returned to near preoperative levels by 3 months after LASIK in group 1 (low to moderate myopia) and by 6 months in the high myopia and hyperopia groups (groups 2 and 3 respectively in our series). This level of return of corneal sensation is probably a useful level of recovery to allow corneal protection by the sensation induced blink and tearing reflexes. This observed time is substantially shorter than the previously reported time of 9.3 months14 and longer than reported by Chuck et al,13 who observed that corneal sensation returned to near preoperative levels by 3 weeks after LASIK.

Kim and co-authors,15 reported that corneal sensitivity did not recover to the preoperative level by 6 months after LASIK.

Table 3  Morphological status of the sub-basal nerve fibre bundles (NFBs) at each time point for the three groups examined

<table>
<thead>
<tr>
<th>Groups</th>
<th>No NFB images</th>
<th>Short, unconnected NFBs</th>
<th>Long NFBs without interconnections</th>
<th>Long NFBs with interconnections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>1 month after LASIK</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3 months after LASIK</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6 months after LASIK</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>1 year after LASIK</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>1 month after LASIK</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 months after LASIK</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6 months after LASIK</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>1 year after LASIK</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>1 month after LASIK</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 months after LASIK</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6 months after LASIK</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1 year after LASIK</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>
except at the hinge of the corneal flap and that the pattern of sensitivity recovery was similar among the various points.

The difference between authors in the time of corneal sensation recovery may be related to two factors: the first is the difference between the groups studied. We found a difference in the corneal sensation recovery time between low to moderate myopia, high myopia, and hyperopia. The second factor is the difference between the authors in the definition of the corneal sensation recovery. Complete corneal sensation recovery, definitely, will take longer than what we call near normal or useful corneal sensation recovery.

At 1 month post-LASIK treatment, corneal sensation in group 2 (the high myopia group) was markedly lower than in group 1 (mild to moderate myopia) and it took 6 months for the corneal sensation to recover to near normal level in group 2 compared to 3 months in group 1. The corneal sensation at one month postoperatively was significantly lower in all eyes than the preoperative level.

One of the reasons for this difference of postoperative corneal sensation between the shallow and deep ablation groups may be the correlation between depth of ablation and nerve damage. The deeper the ablation, the larger the amount of tissue removed from the stroma and the deeper the damage to nerve trunks. Therefore, it is no surprise that the groups with deeper ablation showed a greater decrease in sensation and a longer time for full recovery than did the groups with shallow ablation.

Sub-basal nerve fibre bundles (fig 2A, B, and C), composed of several axons surrounded by a Schwann cell sheath, were easy to identify by confocal microscopy. Consequently, they have become the main objects for evaluation of corneal nerve density by IVCM16 17 and they also serve as a useful landmark between the epithelium and Bowman’s layer. They usually appear as bright, well defined, linear structures. They are sometimes branched, and they usually appear in several consecutive frames but individual nerve fibres cannot be seen with the clinical confocal microscope. Thick stromal nerve bundles (fig 2D) and their side branches, seen as reflecting lines, can easily be imaged, but quantification is difficult because their numbers are small and the same bundles travel through several consecutive 7–10 mm thick optical sections.18

Chiou and co-authors19 identified many linear features by clinical confocal microscopy including vessels, lattice dystrophy, posterior polymorphous dystrophy, and fungal keratitis. However, the only linear structures in normal corneas consisted of nerves. They were well delineated and had homogeneous hyper-reflectivity.

Examination of the regeneration of the subepithelial nerve plexuses after LASIK showed that, firstly, regenerating fibres appeared as short sub-basal leaches. Then by 3 months they were elongated, but interconnections were not observed before the sixth postoperative month.

Correlation between regeneration of sub-basal nerve morphology, as observed by IVCM, and corneal sensitivity, measured by Cochet-Bonnet aesthesiometer, suggested that corneas with no nerve images or short, unconnected nerve fibres, in the sub-basal layer, are associated with lower sensitivities than corneas with long nerve fibres with or without visible interconnections (p<0.001). That agrees with IVCM study of myopic LASIK treated eyes by Linna and co-authors.10

Like other studies,20 we also noted that re-innervation commenced from the margins of the ablation zone toward the centre. That finding explains the greater decrease in sensation in the hyperopia (group 3) and the longer time for full recovery than the mild to moderate myopia (group 1). Disturbance of the sensory reflex arch between the cornea and lacrimal system may have accounted for the fact that a number of patients displayed dry eye symptoms and signs after LASIK. Features typical for dry eye, such as lack of the water component and impaired tear fluid stability, have been described.21 Siganos et al22 found that the tear secretion following LASIK was decreased during 3 months after surgery and was normalised by 6 months.

Wilson23 reported significant punctate epithelial erosions and rose Bengal staining on the flap in 4% of patients at 1–3 months after LASIK. He hypothesised that corneal epithelial rose Bengal staining that develops after LASIK is most likely attributable to LASIK induced (presumed) neurotrophic epitheliopathy, similar to that which is noted in eyes with trigeminal nerve defects caused, for example, by trauma or tumours. In our study we noted that the overall incidence of punctate keratitis was relatively low (15.6%) at 1 month and declined with time, presumably related to recovery of corneal sensations.

Ocular surface disease related to tear fluid abnormalities and/or neurotropic phenomena represent the most common adverse effect of LASIK.24 25 In this respect IVCM can be used to assess postoperative corneas, which show neural damage. IVCM can also be used to differentiate them from eyes with decreased tear secretion, but well regenerated innervation. Moilanen et al26 reported a patient with a very well regenerated sub-basal nerve plexus in the central cornea but still showed subjective dry eye 5 years after PRK.

It is likely that there is a difference between patients in the sensitivity of the corneal epithelium to denervation, with some patients having symptoms of dryness without signs develop, others having symptoms and signs develop, and most having neither symptoms nor signs of epitheliopathy. Individuals with borderline dry eye are known to have an increase in symptoms for variable periods after LASIK treatment and normal individuals may start experiencing symptoms for the first time following LASIK.

Our results agree with the longitudinal studies done by Lee et al27 using the confocal microscopy, which suggest that morphological recovery of corneal innervation may take longer than 12 months after LASIK. In our series, confocal microscopy of the cornea 1 year after LASIK showed that sub-basal NFB did not recover to the preoperative condition even in some patients who had recovered normal corneal sensation. Probably, the number and length of sub-basal NFBs needed for normal corneal sensation are less than the average normal sub-basal NFB density or mechanical corneal sensation measurement is not very accurate.

**CONCLUSION**

After LASIK, corneal sensitivity is decreased in the central cornea for as long as 6 months or more. The results suggest that lamellar cutting of the cornea during LASIK impairs corneal sensitivity and that the depth of the corneal ablation affects the extent of loss of corneal sensitivity and recovery. The diameter of the flap and the ablation area may also have an effect on the degree of corneal sensation loss and time for its recovery. The deeper the ablation and the larger the flap and ablation diameter, the greater the reduction in corneal sensitivity and the longer the time for full recovery. In vivo confocal microscopy revealed LASIK induced alterations of nerve morphology in the sub-basal layer and thus enabled studying the correlation between corneal sensory innervation and sensitivity. A direct positive correlation was found between corneal sub-basal nerve bundle regeneration and corneal sensation recovery. However, as shown in this study, full recovery of the sub-basal NFBs was not achieved by the time of near normal, or useful corneal sensation recovery (6 months after LASIK). Lee et al27 found that at 1 year post-LASIK, the number of sub-basal NFB remained less than half of that before LASIK. Similarly, Muller et al28 stated that near
normal recovery of sub-basal NFB can be expected 2 years after LASIK.

Authors’ affiliations
M A Bragheeth, H S Dia, Division of Ophthalmology and Visual Sciences, University of Nottingham, Nottingham, UK

Proprietary interest: Both authors have no propriety interest in any equipment, method, or technique used or referenced in the manuscript.

REFERENCES
EXTENDED REPORT

Efficiency of blood culture bottles for the fungal sterility testing of corneal organ culture media

G Thuret, A Carricoja, A C Vautrin, H Raberin, S Acquart, O Garraud, P Gain, G Aubert

Background/aim: The consequences of fungal contamination of an organ cultured cornea, though exceptional, are often disastrous for the recipient. Consequently, eye banks often quarantine corneas for 10 days or more before passing them for grafting. This period, though detrimental to the endothelial cell density of the delivered cornea, is necessary to detect contamination using conventional microbiological methods. The authors previously validated the use of a pair of aerobic and anaerobic blood bottles for sensitive and rapid detection of bacteria. To allow a short quarantine period, it remained only to optimise detection of fungi. The authors aimed to compare sensitivity and rapidity of fungal contamination detection by three methods: blood bottles, Sabouraud, and daily visual inspection of the organ culture medium.

Methods: Four inocula ($10^6$, $10^5$, $10^4$, 10 colony forming unit [CFU] per ml) of 11 fungi (Candida albicans, C tropicalis, C glabrata, Saccharomyces cerevisiae, Rhodotorula rubra, Cryptococcus neoformans, Fusarium oxysporum, Aspergillus niger, A flavus, Acremonium falciforme) were inoculated in a commercial organ culture medium containing a coloured pH indicator (CorneaMax, Eurobio, Les Ulis, France). The real live fungal inoculum was verified immediately after inoculation. After 48 hours at 31˚C, samples of the contaminated media were inoculated in three blood bottles: Bactec Aerobic/F, Bactec Mycosis IC/F, and Bactec Myco/F Lytic (Becton Dickinson, Le Pont de Claix, France), then placed in a Bactec 9240 rocking automat, and in four Sabouraud media (solid and liquid, 28˚C and 37˚C) with daily observation. Contaminated organ culture media were also checked daily for any change in turbidity and/or colour. Experiments were performed in triplicate.

Results: Mycosis IC/F and Myco/F Lytic bottles were neither faster nor more sensitive than the aerobic bottle. The three methods were positive for all inocula, even the lowest (visible inoculum below 10 CFU/ml for each fungus). Contamination was detected within 24 hours by the aerobic bottles in 91% (40/44), by Sabouraud in 98% (43/44) (no significant difference) and by visual inspection in 66% of cases (29/44) (p<0.001 with the two others). Maximum times to detection were 46, 48 and 72 hours respectively.

Conclusion: This study further counters the preconception that fungal contamination is hard to detect in corneal organ culture media. This study is the last step in validating the use of a pair of blood bottles for the sterility testing of organ culture media, this time for fungi. Their use should make it possible to shorten microbiological quarantine and thus deliver corneas with higher endothelial cell density, without increasing the risk of recipient contamination.

Materials and methods

The experiment design, presented in figure 1, reproduces that used in our previous study on bacterial contamination.

Abbreviations: CFU, colony forming unit
Micro-organisms
Eleven fungi present in postmortem eye flora and/or implicated in post-graft endophthalmitis or keratomycosis, generally after storage at +4°C or more rarely in organ culture, were studied. Strains were obtained either from the American Type Culture Collection (ATCC) (Rockville, MD, USA) or the Pasteur Institute (Paris, France): Candida albicans 90028, C. tropicalis 66029, C. glabrata ATCC 66032, Saccharomyces cerevisiae ATCC 9763, Rhodotorula rubra ATCC 66034, Cryptococcus neoformans 212146, Fusarium oxysporum 625-72, Aspergillus niger 980463435, A. fumigatus 864-64, A. flavus 97467, Acremonium falciforme 7761.

Four decreasing inocula (10⁶, 10⁴, 10², 10 colony forming unit/ml (CFU/ml) of each fungus were inoculated in two 100 ml bottles of commercial organ culture medium (CorneaMax, Eurobio, Les Ulis, France). The real inoculum was immediately determined by seeding 100 μl of contaminated medium on a Sabouraud medium and counting colonies on the dish. The inoculated organ culture media were incubated in two sealed flasks for 48 hours at 31°C in a conventional carbon dioxide free dry incubator. This simulated the initial 2 day quarantine that most European banks routinely observe before the first microbiological tests and sometimes also the first endothelial assessment. The first bottle was then used for culturing on Sabouraud media and blood bottles, and the second was reserved for the visual method and kept closed.

Microbiological protocols
In the visual method, changes in colour (to orange or yellow) or turbidity (including the growth of a filamentous fungus in an otherwise clear red medium) of the organ culture medium, indicating positivity, were screened daily by visual inspection until detection. In the Sabouraud method, 1 ml of contaminated organ culture medium was inoculated in two Sabouraud agars and in two Sabouraud broths (10 ml). One Sabouraud set was incubated at 28°C, the other at 37°C. Growth was screened daily by visual inspection until positivity. In the blood bottle method, 2.5 ml of contaminated organ culture medium was injected into one Bactec Plus Aerobic/F and two bottles designed for fungal detection: a Bactec Mycosis IC/F and a Bactec Myco/F Lytic (Becton Dickinson, Le Pont de Claix, France). Exceptionally in this series (see below), in the absence of growth of C. glabrata in the aerobic bottle, one Bactec Lytic/10 Anaerobic/F bottle was added for this strain. The bottles were placed in a Bactec 9240 incubator at 35°C and rocked continuously. The incubator detected any rise in carbon dioxide produced by fungal growth. A sensor placed at the bottom of each bottle reacted with the carbon dioxide and produced fluorescence.
RESULTS

The real inocula varied by less than 10–15×10^6 CFU/ml. The inoculated fungi always corresponded to the one detected, thus ruling out any exogenous contamination during manipulation by the technician.

Performance comparison of the three blood bottles

The three blood bottles detected all 11 fungi except C glabrata, whose growth was inconsistently detected by the aerobic bottle (only three out of the 12 assays). However, this yeast was always detected by the two fungal bottles and the anaerobic bottle. Times to detection in hours and percentage of detection within 24 hours following the inoculation, which in practice reflect the working hours of a hospital microbiology laboratory (see paragraph below), are presented in table 1. When comparing these percentages, there was no significant difference between the Aerobic/F and Mycosis IC/F bottles (p = 1). The Myco/F Lytic tended to be less effective, but the difference observed did not reach the significance threshold (p = 0.080 for Aerobic/F and p = 0.156 for Mycosis IC/F). No blood bottle tested positive without an identifiable germ, thus ruling out the possibility of a false positive having been generated by a physicochemical reaction of the organ culture medium with the contents of the bottle. The results obtained with the aerobic bottle, which tends to be the most effective of the three and in any case routinely used for bacteria, were then compared with the other two microbiological methods.

Sensitivity and rapidity of the three methods (fig 2)

The three methods were positive for all inocula of all fungi, even the lowest (numbered systematically ≤10 CFU/ml) for each of the 11 fungi. No control medium was positive.

To compare the three methods, whose times to detection were not in practice measured in the same way (automatic measurement every 10 minutes for the blood bottles, and screening by a technician every 24 hours for the other two methods) we only considered the positivity rates within 24 hours. This reflects the reality of a microbiology laboratory or eye bank, with detection during working hours from the day after inoculation. Visual inspection detected contamination within 24 hours in only 66% of cases (29/44), whereas Sabouraud (solid or liquid, whatever the temperature) detected it in 98% (43/44), and the Aerobic/F bottle in 91% of cases (40/44). Visual inspection was thus significantly slower than the other two methods (p < 0.001), whereas the difference between Sabouraud and the Aerobic/F bottle was insignificant (p = 0.360). Maximum times to detection for visual inspection, Sabouraud and the Aerobic/F bottle were 72, 48, and 46 hours respectively. With visual inspection, the maximum time to detection was for the lowest inocula of Saccharomyces cerevisiae and Cryptococcus neoformans, detected by Sabouraud and the Aerobic/F bottle in 24 and 46 hours and 24 and 20 hours, respectively. The only case of Sabouraud positive in 48 hours was for the lowest inoculum of Acremonium falciforme, which was detected by the Aerobic/F bottle in 20 hours. The maximum time to detection by the Aerobic/F bottle (46 hours) was for the lowest inoculum of Saccharomyces cerevisiae, detected in 24 hours by Sabouraud.

DISCUSSION

This experimental study of the main fungi in postmortem eye flora and/or responsible for several ocular infection complications that are found on bacteria.² It validates the use of a pair of aero/anaerobic blood bottles to ensure the microbiological safety of organ culture stored corneas. The three test bottles detected the very low fungal inocula (≤10 CFU/ml), which probably corresponds to those found clinically in donors and remaining after decontamination by povidone-iodine. Our methodology, with preparation of inoculum by dilution and immediate verification of the real live inoculum, allowed confirmation that very low starting inoculum had been cultured. These inocula were even lower than those described by Rousset et al, who studied the effectiveness of the visual and Sabouraud methods.¹¹ As expected, the aerobic bottle proved very effective on its own for all strains except Candida glabrata. This yeast is difficult for aerobic bottles to detect, as described by studies of series of experimental septicaemias and actual ones.¹² However, the yeast was detected by the other blood bottles, particularly the anaerobic one, which is routinely used for bacterial detection in a growing number of French and European eye banks. However, the conventional (Sabouraud, whichever type) and visual methods never appeared inadequate for fungal detection, contrary to our previous study on bacteria using a similar design.³ That study showed that the main advantage of the aero/anaerobic blood bottle pair over conventional microbiological techniques or visual inspection is its rapid detection of contamination. This also applies to fungi, because detection by aerobic bottle was obtained in a mean 13 hours (maximum 46). However, this short time was a less decisive advantage than with bacteria. If we reason in laboratory technicians’ working hours, time to detection by the other two methods is comparable because detection can always be obtained 1 or 2 days after inoculation (weekends excepted). It was thus necessary to demonstrate that the benefit in terms of rapidity of bacterial detection was not achieved to the detriment of its effectiveness to detect fungi. The present study proves that the pair of blood bottles must be effective enough to allow risk free discontinuation of the Sabouraud medium, which moreover is time consuming for technicians.

Table 1 Comparison of the three blood bottles. Both times to detection in hours and percentage of detection within the 24 hours following inoculation were presented. Results were means of experiments performed in triplicates.

<table>
<thead>
<tr>
<th></th>
<th>Aerobic/F</th>
<th>Mycosis IC/F</th>
<th>Myco/F Lytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to detection (mean (SD), median, range)</td>
<td>13 (9), 13, 1–46</td>
<td>14 (19), 11, 1–108</td>
<td>22 (24), 14 (5–114)</td>
</tr>
<tr>
<td>% of detection within 24 hours (n)</td>
<td>91% (40/44)</td>
<td>89% (39/44)</td>
<td>77% (34/44)</td>
</tr>
</tbody>
</table>

www.bjophthalmol.com
Importantly, all three techniques allowed detection of the lowest inoculum of all the tested fungi within 3 days. Contaminated corneas could thus be very quickly removed from the incubator, minimising the risk of contamination of the bank environment. The high capacity of conventional methods for detecting fungal contamination was stressed by Rousset et al. Note that neither Rousset’s study (on, notably, four fungi not tested in our study; Candida parapsilosis, Aspergillus fumigatus, Aspergillus niger, Aspergillus flavus, Rhodotorula rubra, Cryptococcus neoformans, Candida albicans, Candida tropicalis, Acremonium sp, Fusarium sp) nor our own (which tested Saccharomyces cerevisiae, Rhodotorula rubra, Aspergillus niger, not studied by Rousset) did not highlight difficulties in rapid detection of fungal contamination. Inocula were very low in both studies: 10 elements per bottle for Rousset and less than 10 CFU/ml of viable inoculum in our study. These studies invalidated older ones, which raised the fear of late development of pathogenic fungi and so justified prolonged quarantine of graft tissue. Shorter quarantine is currently an important objective, at least in certain penetrating keratoplasty indications. It has been clearly shown that, to increase graft tissue survival in recipients, it is preferable to deliver corneas with the highest possible endothelial cell density. This particularly applies to recipients with high endothelial cell density and a low risk of rejection, such as those with keratoconus, currently one of the main indications for cornea graft in Europe.

Lastly, although a pair of aero/anaerobic bottles costs more than conventional media, the reduction in technician time allowed by task automation is ultimately cost effective and may be a considerable advantage, particularly for banks that analyse large quantities of storage liquids.

CONCLUSION

The use of a pair of Bactec aerobic and anaerobic blood bottles placed in an automat has enabled us to eliminate the use of Sabouraud medium and, more than 1 year ago, to reduce quarantine by 5 days. Our patients have thus received corneas with higher endothelial cell density without compromising their bacterial or fungal safety. To remain vigilant, particularly in the hypothesis of exceptional contamination by fungi other than those tested in the present study, we still use a Mycosis/IF bottle, the most effective after the aerobic bottle in our study. We will continue this practice until an observational study of the long term cost/benefit ratio, as for bacteria, proves whether it should be discontinued.

ACKNOWLEDGEMENTS

We thank the “Direction Regionale de la Recherche Clinique (Pr H Decousus)” for funding. Grant: Bellevue Hospital 2002 local invitation to tender.

REFERENCES

Bacteria and fungi. 


Use of simulated blood cultures for time to detection comparison between BacT/Alert and Bactec 9240 blood culture systems. Diagn Microbiol Infect Dis 2002; 44:239–40.


Infected keratitis in older patients: a 4 year review, 1998–2002

T K H Butler, N A Spencer, C C K Chan, J Singh Gilhotra, K McClellan

Background/aim: There are few clinical series in the literature of infective keratitis in the elderly, even though this age group constitutes a significant proportion of those affected by this condition. The authors aimed to determine the incidence and risk factors for infective keratitis in those over 60 years, the causative organisms, antibiotic susceptibilities, visual and tectonic outcome, and surgical intervention rate. Methods: A retrospective review of all patients aged 60 years and over admitted to the Sydney Eye Hospital with a diagnosis of infective keratitis, between September 1998 and December 2002. Results: 190 patients were identified with a mean age of 75.5 (SD 9.6) years (range 60–101). Local risk factors were found in 93.7%, and systemic risk factors in 27.9%. Organisms were cultured in 62.8%, and 7.9% had positive herpes simplex virus (HSV) polymerase chain reaction (PCR). Perforation or severe thinning occurred in 36% overall, but in 80% with positive HSV PCR. Acute surgical intervention was required in 43.7%, with acute penetrating keratoplasty performed in 17.9%, and 8.9% required evisceration. Mean presenting visual acuity was 1.82 (SD 1.24), equivalent to 6/300, excluding 26.3% with vision of light perception (LP) or worse. Mean final visual acuity was 1.24 (SD 1.16), equivalent to 6/100, excluding 19.5% with vision of LP or worse ($p<0.0005$). Conclusions: The elderly represent a distinct clinical group in the context of microbial keratitis. Predisposing factors are very common, they present with poor vision, have a high complication and surgical intervention rate, and a poor visual outcome compared to younger patients. The microbiological spectrum is similar to younger age groups, except that HSV is more common and may increase the risk of severe corneal thinning and perforation. Most bacterial isolates remain sensitive to currently available antibiotic preparations.

Infective keratitis is a significant cause of blindness and preventable ocular morbidity worldwide. There are many published series of infective keratitis from both temperate and tropical parts of the world, and management strategies are well established. However, infective keratitis continues to be an important cause of hospital admission, particularly among vulnerable patient groups such as the elderly. With increasing numbers of those of retirement age, the demands this group place on healthcare systems worldwide will continue to rise. Despite this, there are only two published studies of infective keratitis in the elderly population: the first from the United States, a series from over 20 years ago, and more recently, one from rural southern India.

The elderly represent a distinct clinical group in the context of microbial keratitis, as they are less likely to be contact lens wearers (except in aphakia) than younger patients, they are more likely to have had previous or co-existent ocular disease or surgery, and the visual prognosis is significantly worse in older patients. Musch et al showed a bimodal age distribution for infective keratitis with two distinct peaks of incidence, one around the age of 30, and another at 70 years.

The purpose of this study was to identify in those over 60 years, the risk factors for infective keratitis, the microbiological spectrum, and the visual and tectonic outcome, over a 4 year period at a single tertiary referral centre in south eastern Australia.

PATIENTS AND METHODS

All patients aged 60 years and over who were admitted to the Sydney Eye Hospital between September 1998 and December 2002 with a diagnosis of infective keratitis were included in the study. Cases were identified from the database of clinical codes, based on the primary and other diagnoses, recorded for each patient on discharge from the hospital.

Medical records were then retrieved and the data recorded on a standardised form. The data set included details of patients’ age, sex, length of hospital admission, treatment before admission, identifiable local and systemic risk factors, pre-existing ocular disease, other medical history, clinical features, investigations performed, organisms identified, antibiotic sensitivities, treatment and duration of treatment, complications, acute and other surgical interventions, final diagnosis, presenting and final visual acuity, and length of follow up.

Visual acuity was documented in Snellen format, and converted into logMAR equivalent values for analysis. Presenting and final visual acuities were compared using two tailed, paired Student’s $t$ test. Those with visual acuity of light perception (LP) or worse were excluded from mean calculations, but stated separately, as these levels of visual acuity cannot be assigned geometric mean values.

Corneal scrapes were routinely performed on admission with a flame sterilised Kimura spatula or a sterile scalpel blade, placing the specimen onto slides for Gram stain, and direct inoculation of culture media: horse blood agar for aerobic and anaerobic culture, chocolate agar, cooked meat broth, and Sabouraud’s dextrose agar for fungi. If Acanthamoeba was suspected, non-nutrient agar seeded with Escherichia coli was also inoculated. In addition, if clinically indicated, patients were tested for herpes simplex virus and comparable infections.
(HSV) using direct fluorescent antibody (DFA) assay, viral culture, or more recently polymerase chain reaction (PCR).

The media were sent to the South Eastern Area Laboratory Services (SEALS) at the Prince of Wales Hospital, Randwick, NSW, for culture and antibiotic susceptibility. All bacterial isolates were identified using conventional laboratory techniques and stored at $-70^\circ$C. The minimum inhibitory concentration (MIC) of selected antibiotics was determined on each isolate using an agar dilution technique, which conformed to the recommendations of the International Collaborative Study on Antibiotic Sensitivity Testing.

RESULTS

Over the 4 year study period we identified 190 patients for inclusion in the study. Medical records were available for all patients. There were 103 (54%) male and 87 (46%) female patients, with a mean age of 75.5 (SD 9.6) years (range 60–101). The age distribution is shown in figure 1, which shows that although, overall, males are slightly over-represented, beyond the age of 80 there is a female preponderance. The peak incidence occurred in the winter months of June–August, during which there were 73 (38%) admissions (fig 2). The mean length of hospital admission was 17.6 (SD 13.1) days.

Predisposing factors

At least one local risk factor was present in 178 (93.7%) patients (table 1), with more than one risk factor in 42 (22.1%). Previous ocular surgery was the most prevalent risk factor, occurring in 88 (46.3%) patients, but note the small numbers of patients with a history of trauma (3.7%), or contact lens wear (1.1%), as shown in table 1. Systemic risk factors were identified in 53 (27.9%) patients. These are summarised in table 2.

Microbiology

Corneal scrapes were taken for microbiological investigation in 172 (90.5%) patients. In addition, 66 (34.7%) patients were tested variously for HSV as follows: 42 (22.1%) with PCR, 32 (16.8%) with DFA assay, 20 (10.5%) with viral serology, and four (2.1%) with viral culture.

In only 25 (14.5%) patients were organisms identified on the Gram stain, most of these being Gram positive cocci (16), with Gram positive bacilli in five cases, and Gram negative bacilli in five cases, and multiple types in two patients. Organisms were cultured in 108 (62.8%) of those where scrapes were taken, with more than one organism in 12 (11.1%) of those culture positive patients. The types of organism identified are shown in table 3, and the antibiotic susceptibilities as stated in the laboratory reports, are shown in table 4. Topical antibiotics had been used before presentation in 25 (39.1%) of the culture negative patients, and 41 (38.0%) of culture positive patients.

Fifteen of the 42 patients (36%) tested with HSV-PCR were positive. Of these 15 positive patients, nine (60%) had no previous history of herpetic eye disease, and seven (47%)...
The mean duration of topical antibiotic treatment was 3.8 (2.9) weeks (excluding postoperative prophylactic antibiotics). Initial antibiotic treatment was modified in 28 (14.7%) patients in light of microbiology results.

Acute surgical intervention was required in 83 (43.7%) patients (table 7), with acute penetrating keratoplasty (PK) performed in 34 (17.9%), and 17 (8.9%) requiring removal of the eye. Of the 14 patients who were culture positive for *Pseudomonas* sp, nine (64%) required some surgical intervention, with loss of the eye in three (21%), and acute PK in three (21%) patients.

### Complications
Complications occurred in 93 (48.9%) patients overall, with more than one complication in 11 (5.8%). Details are summarised in table 8.

### Visual outcome
Mean presenting visual acuity was 1.82 (1.24), equivalent to 6/300, excluding 50 (26.3%) patients with vision of LP or worse. Mean visual acuity at last follow up was 1.24 (1.16), equivalent to 6/100, excluding 37 (19.5%) patients with vision of LP or worse (*p*<0.0005). Table 9 summarises the visual outcome among the viral and non-viral keratitis groups. There were 36 (18.9%) patients with visual acuity of at least 6/12 at last follow up, compared to 13 (6.8%) at presentation, and 79 (41.6%) patients who had visual acuity of worse than 6/60 at last follow up. Importantly, this left 16 (8.4%) patients legally blind because of pre-existing contralateral poor vision.

### DISCUSSION
#### Patient demographics
The elderly make up a significant proportion of patients admitted to hospital with severe infective keratitis. We found 190 patients of 60 years and over with this diagnosis admitted to the Sydney Eye Hospital, a large tertiary referral teaching hospital, over a 4 year period. Over the same period, a total of 426 patients were admitted to our unit with this diagnosis. Those over 60 therefore constitute 45% of total admissions for infective keratitis at our unit.

Kunimoto *et al* studied 102 cases of microbial keratitis in the over 65s, over a 4 year period, at a tertiary referral centre in rural southern India. Their group had a mean age of 69, with a significant male preponderance (70.6%). The setting of that study, in a rural tropical region of southern India, contrasts with our study in the temperate zone of Sydney, Australia. We found only a minimal male preponderance (70.6%). The setting of our group, compared to over 70% in the study by Kunimoto, and we found, beyond the age of 80, females were over-represented. This may be because, in our study, 70 (36.8%) patients were 80 years or over, compared to only six (5.9%) patients in the study by Kunimoto. In the only previous study

---

**Table 3** Organisms cultured

<table>
<thead>
<tr>
<th>Organism</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus sp</td>
<td>52</td>
<td>47.2</td>
</tr>
<tr>
<td>Coagulate negative Staphylococcus</td>
<td>30</td>
<td>27.8</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>22</td>
<td>20.4</td>
</tr>
<tr>
<td>Streptococcus sp</td>
<td>13</td>
<td>12.0</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>6</td>
<td>5.6</td>
</tr>
<tr>
<td><em>β haemolytic Streptococcus</em></td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>Corynebacterium sp</td>
<td>14</td>
<td>6.5</td>
</tr>
<tr>
<td>Other Gram positive</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>Total Gram positive</td>
<td>82</td>
<td>75.9</td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp</td>
<td>14</td>
<td>13.0</td>
</tr>
<tr>
<td><em>P aeruginosa</em></td>
<td>12</td>
<td>11.1</td>
</tr>
<tr>
<td>Bacillus sp</td>
<td>4</td>
<td>3.7</td>
</tr>
<tr>
<td>Moraxella sp</td>
<td>5</td>
<td>4.6</td>
</tr>
<tr>
<td>Other Gram negative</td>
<td>5</td>
<td>4.6</td>
</tr>
<tr>
<td>Total Gram negative</td>
<td>28</td>
<td>25.9</td>
</tr>
<tr>
<td>Fungi</td>
<td>4</td>
<td>3.7</td>
</tr>
<tr>
<td>Nocardia sp</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Acanthamoeba</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>More than 1 organism</td>
<td>12</td>
<td>11.1</td>
</tr>
<tr>
<td>Total with positive culture</td>
<td>108</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 4** Antibiotic susceptibilities

<table>
<thead>
<tr>
<th></th>
<th>Chloramphenicol</th>
<th>Ciprofloxacin</th>
<th>Gentamicin</th>
<th>Penicillin</th>
<th>Cephalothin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No %</td>
<td>No %</td>
<td>No %</td>
<td>No %</td>
<td>No %</td>
</tr>
<tr>
<td>Staphylococcus sp</td>
<td>35 (41)</td>
<td>25 (28)</td>
<td>89.3</td>
<td>3 (7)</td>
<td>13 (43)</td>
</tr>
<tr>
<td>Staph aureus</td>
<td>15 (16)</td>
<td>93.8</td>
<td>83.3</td>
<td>1 (4)</td>
<td>11 (36)</td>
</tr>
<tr>
<td>Coag negative Staphylococcus</td>
<td>20 (25)</td>
<td>80.0</td>
<td>15 (12)</td>
<td>93.8</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Streptococcus sp</td>
<td>8 (8)</td>
<td>100.0</td>
<td>2 (2)</td>
<td>100.0</td>
<td>0 (2)</td>
</tr>
<tr>
<td>Corynebacterium</td>
<td>6 (8)</td>
<td>75.0</td>
<td>6 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp</td>
<td>–</td>
<td>12 (12)</td>
<td>100.0</td>
<td>14 (14)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Numbers shown are number of sensitive isolates (total tested).
* Ceftazidime.
Percentages are percentage of sensitive isolates.
of microbial keratitis in the elderly from a temperate region, Ormerod studied only bacterial keratitis in 142 patients aged 65 years and over, between 1977 and 1984 at several centres in Boston and Los Angeles, United States. He found an equal sex distribution.

Predisposing factors

The vast majority (94%) of our patients had at least one identifiable risk factor. This is in common with previous age independent studies where risk factors were identified in 88–91% although the overall proportion of patients with identifiable risk factors is not stated in the studies by Ormerod or Kunimoto in the elderly.

However, in older patients the types of risk factors differ from younger age groups. Contact lens wear and trauma, common among younger groups, were uncommon in our series, but previous ocular disease and surgery accounted for the majority. This compares with Ormerod’s findings, where the leading risk factors were: use of topical corticosteroids (38%), corneal scarring (33%), contact lens wear (25%), and bullous keratopathy (19%). Much less frequent were trauma (5%), and “recent” cataract surgery (4%), although the number who had undergone previous ocular surgery is not stated. The use of contact lenses among the elderly has declined since the study by Ormerod from 25 years ago, with the advent of more modern cataract surgery techniques, and far fewer aphakic patients. Kunimoto et al found previous ocular disease (35%), and previous ocular surgery (29%) to be the main risk factors, very few contact lens wearers (2%) as in our study, but found a high rate of trauma (18%) among their group from rural India.

Unsurprisingly, systemic risk factors are also more common in the elderly, present in 28% of our cases. Ormerod found 28% with systemic risk factors, compared to 17% among the group of Kunimoto et al. In contrast, Bourcier et al found systemic predisposing factors in only 5.8% in their series of 291 patients with a mean age of 39.

These represent only those risk factors that are readily definable and measurable. Other factors such as mobility, access to health care, support network, socioeconomic factors, dexterity, and compliance will undoubtedly have an important impact on the older patient, and therefore their susceptibility to disease and response to treatment. These are much less easily assessed, and the risk factors stated in this study, are therefore probably an underestimate in the overall context of these patients’ disease.

Microbiology

Our culture positive rate of 63% is similar to previous reports, and 76% of cultured organisms were Gram positive in our series. In this study, we found that the microbiological spectrum is similar to recent age independent series from temperate regions of the world. It is interesting that the common pathogens of the outer eye have remained relatively constant for decades, with similar results reported by Musch et al and Ormerod 25 years ago. The latter found 66% were Gram positive, with the leading organisms being coagulase negative staphylococci (23%), Staphylococcus aureus (23%), Streptococcus pneumoniae (14%), and Pseudomonas aeruginosa (20%). Goldstein et al reported a decrease in the proportion of Gram positive bacterial keratitis over the past decade, and postulated that the rise in the empirical use of fluoroquinolones in the community, may have had an effect on culture rates and patterns. However, in a similar study, Alexandrakis et al found no such trend.

HSV was implicated in 43 (22.6%) patients. In 15 patients (7.9%) PCR for HSV was positive, suggesting active infection. Interestingly, 60% of these had no previous history of herpetic eye disease, and in half, HSV was the only organism identified. PCR has previously been shown to be a sensitive method for the detection of HSV in keratitis. Although the numbers are small in this series, it would seem that PCR has a higher detection rate for HSV than DFA assay. Of the 19 tested by both methods, nine (47%) were positive on PCR, but all were negative on DFA assay.

Previous studies in the elderly have excluded HSV keratitis. Our series shows significant morbidity associated with HSV in the elderly, either as a predisposing factor, in polymicrobial infection, or as the single causative pathogen. Previous age independent series of microbial keratitis have tended to focus on bacterial causes, but rates of 1.8–2.0% for...
HSV have been reported. It might be expected that as immunity reduces with age, the impact of herpetic eye disease may increase. Certainly a high index of suspicion for HSV as a contributor or cause of keratitis must be maintained in the elderly.

### Treatment
All the main bacterial species were sensitive to at least one of the most commonly used antibiotics, although the numbers were small among some of the groups tested. In particular, we found no resistance of Pseudomonas to ciprofloxacin, gentamicin, or ceftazidime among those tested. Hyndiuk et al. have shown fluoroquinolone monotherapy to be clinically and statistically equivalent to standard dual fortified antibiotic therapy in bacterial keratitis in a randomised, double masked, multi centre trial. However, there have been several reports showing increasing resistance to fluoroquinolones, particularly among Streptococcus sp.,10 14 19 coagulase negative staphylococci,10 12 19 and Pseudomonas sp.20 We found some resistance to ciprofloxacin among the staphylococci isolated, but the majority remained sensitive. In a retrospective review of 138 cases, Gangopadhyay et al.13 reported an increased incidence of corneal perforation among those treated with fluoroquinolone monotherapy compared to standard dual fortified antibiotic therapy, and cautioned the use of fluoroquinolone monotherapy in severe keratitis, particularly in the elderly.

Our data support the initial empirical use of intensive fortified cephalosporin and gentamicin as first line therapy in the elderly, which the majority of our patients received. Fluoroquinolone monotherapy should perhaps not be first choice, given the resistance among some staphylococci, which was the most frequently identified organism in our series, although in vitro resistance does not necessitate lack of clinical response.

The high surgical intervention rate of 43.7% in our series is higher than reported by Ormerod (29%), although similar to Kunimoto et al. (41.2%). These rates from series among the elderly are much higher than in age independent series where rates of 1.3–21.4% are reported. It is likely that delayed presentation, poor nutrition or hydration, reduced immunity, co-existent disease, and poor healing contribute to the higher rate among the elderly.

### Complications
Almost half the patients in our series had at least one complication. There was a high rate of perforation (12.1%), and this is reflected in the high rates of acute keratoplasty and removal of the eye. Interestingly, perforation or severe thinning occurred in 30% overall, but in over 70% of those with positive HSV PCR. This diagnosis should therefore be suspected in those who develop threatened or actual perforation. Previous series in the elderly have reported high rates of enucleation/evisceration (7% and 14.7%), which compares to our rate of 8.9%, whereas age independent series report rates of less than 1%.

### Visual outcome
Previous studies of infective keratitis in the elderly have not commented on presenting visual acuity. The patients in this series had a very poor presenting mean visual acuity (6/300), excluding over 25% having LP or worse. This is unlike younger patients: Wong et al. reported mean presenting visual acuity of 0.86 (equivalent to 6/36–6/48), and Bourcier et al. reported 0.51 (6/18–6/24). Our study also highlights the poor visual outcome of infective keratitis in the elderly, with over 40% worse than 6/60, and almost 20% LP or worse at last follow up. Kunimoto et al. also found a poor outcome among the elderly with 75% worse than 20/400. Younger patients do much better, with Wong et al. reporting a mean final visual acuity of 0.36 (6/12–6/15).

### CONCLUSIONS
The present study is limited by its retrospective design, the lack of a younger control group, and the heterogeneity of this difficult patient group who have multiple associated factors. It is also based on patients who were admitted to hospital, as is frequently necessary in older patients, but this will select

---

**Table 7** Acute surgical interventions (numbers shown are number of patients (%))

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Viral</th>
<th>Mixed*</th>
<th>Non-viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetrating keratoplasty</td>
<td>34 (17.9)</td>
<td>8 (25.8)</td>
<td>2 (16.7)</td>
<td>24 (16.3)</td>
</tr>
<tr>
<td>Tarsorrhaphy</td>
<td>26 (13.7)</td>
<td>4 (12.9)</td>
<td>0 (0.0)</td>
<td>22 (15.0)</td>
</tr>
<tr>
<td>Evisceration/enucleation</td>
<td>17 (9.0)</td>
<td>1 (3.2)</td>
<td>0 (0.0)</td>
<td>16 (10.9)</td>
</tr>
<tr>
<td>Corneal glue</td>
<td>9 (4.7)</td>
<td>7 (22.6)</td>
<td>0 (0.0)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Conjunctival flap</td>
<td>5 (2.6)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Amniotic membrane graft</td>
<td>3 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Lamellar keratoplasty</td>
<td>2 (1.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Botulinum toxin phasis</td>
<td>2 (1.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>None</td>
<td>107 (56.3)</td>
<td>12 (38.7)</td>
<td>9 (75.0)</td>
<td>86 (58.8)</td>
</tr>
<tr>
<td>Any</td>
<td>83 (43.7)</td>
<td>19 (61.3)</td>
<td>3 (25.0)</td>
<td>61 (41.5)</td>
</tr>
<tr>
<td>Total</td>
<td>190</td>
<td>31</td>
<td>12</td>
<td>147</td>
</tr>
</tbody>
</table>

*Mixed viral and bacterial keratitis.

---

**Table 8** Complications (numbers shown are number of patients (%))

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Viral</th>
<th>Mixed*</th>
<th>Non-viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarring (visually significant)</td>
<td>47 (24.7)</td>
<td>6 (19.4)</td>
<td>3 (25.0)</td>
<td>38 (25.9)</td>
</tr>
<tr>
<td>Persistent epithelial defect</td>
<td>25 (13.2)</td>
<td>5 (16.1)</td>
<td>0 (0.0)</td>
<td>20 (13.6)</td>
</tr>
<tr>
<td>Perforation</td>
<td>23 (12.1)</td>
<td>10 (22.3)</td>
<td>1 (8.3)</td>
<td>12 (2.2)</td>
</tr>
<tr>
<td>Loss of eye</td>
<td>17 (8.9)</td>
<td>1 (3.2)</td>
<td>0 (0.0)</td>
<td>16 (10.9)</td>
</tr>
<tr>
<td>Raised IOP/glaucoma</td>
<td>6 (3.2)</td>
<td>2 (6.3)</td>
<td>0 (0.0)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Cataract</td>
<td>4 (2.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2.1)</td>
<td>3 (9.7)</td>
<td>1 (8.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Any complication</td>
<td>93 (48.9)</td>
<td>24 (77.4)</td>
<td>5 (41.7)</td>
<td>64 (43.5)</td>
</tr>
<tr>
<td>More than 1 complication</td>
<td>11 (5.8)</td>
<td>2 (6.5)</td>
<td>0(0.0)</td>
<td>9 (6.1)</td>
</tr>
</tbody>
</table>

*Mixed viral and bacterial keratitis.*
for patients with more severe disease. However, this study confirms the elderly represent a distinct clinical group in the context of microbial keratitis. Predisposing factors are very common, they present with poor vision, had a high complication and surgical intervention rate, and a poor visual outcome compared to younger patient groups. The microbiological spectrum is similar to that seen in the younger population, except that HSV is more common and may increase the risk of severe corneal thinning and perforation. Most bacterial isolates remain sensitive to currently available antibiotic preparations.

ACKNOWLEDGEMENTS
We acknowledge the support of the Sydney Eye Hospital Foundation, and the Save Sight Institute, University of Sydney.

Authors’ affiliations
T K H Butler, N A Spencer, C C K Chan, J S Gilhotra, K McClellan, Department of Clinical Ophthalmology and Save Sight Institute, University of Sydney, GPO Box 4337, Sydney, NSW, 2001, Australia

Competing interests: none declared

REFERENCES

Table 9  Visual outcome among viral and non-viral patient groups

<table>
<thead>
<tr>
<th></th>
<th>Mean preop visual acuity*</th>
<th>SD</th>
<th>Mean postop visual acuity*</th>
<th>SD</th>
<th>p Value</th>
<th>Presentation</th>
<th>Last visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1.82 (6/300)</td>
<td>1.24</td>
<td>1.24 (6/100)</td>
<td>1.16</td>
<td>&lt;0.0005</td>
<td>50 (26.3)</td>
<td>37 (19.5)</td>
</tr>
<tr>
<td>Viral</td>
<td>2.12 (6/600)</td>
<td>1.15</td>
<td>1.56 (6/200)</td>
<td>1.28</td>
<td>0.10</td>
<td>4 (9.3)</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td>Non-viral</td>
<td>1.69 (6/300)</td>
<td>1.26</td>
<td>1.13 (6/86)</td>
<td>1.11</td>
<td>&lt;0.0001</td>
<td>46 (31.3)</td>
<td>34 (23.1)</td>
</tr>
</tbody>
</table>

*LogMAR visual acuity (approximate Snellen equivalent)
†Light perception (LP) or worse vision, excluded from mean calculations.

Filtering bleb function after clear cornea phacoemulsification: a prospective study

J Klink, B Schmitz, W E Lieb, T Klink, H-J Grein, J Sold-Darseff, A Heinold, F Grehn

EXTENDED REPORT

Aim: To evaluate the influence of clear cornea phacoemulsification on filtering bleb morphology, function, and intraocular pressure (IOP) in glaucomatous eyes with previously successful filtering surgery.

Methods: The clinical course of 30 patients (30 eyes) who underwent clear cornea phacoemulsification after successful filtering glaucoma surgery was prospectively evaluated. Mean IOP and filtering bleb morphology (standardised assessment criteria and score 0–12, 12 = optimum) were determined before surgery, and 3 days, 6 months, and 12 months after surgery. The control group consisted of 36 patients with glaucoma after clear cornea phacoemulsification without previous filtering surgery.

Results: Mean IOP increased after phacoemulsification by about 2 mm Hg (preoperatively 14.28 (SD 3.71) mm Hg, 12 months postoperatively 16.33 (3.31) mm Hg, p = 0.006). 15 patients (50%) showed an IOP increase of >2 mm Hg, 11 patients (36.7%) had no IOP difference (within 2 mm Hg), and in four patients (13.3%) IOP decreased >2 mm Hg. Mean score of filtering bleb morphology 1 year after surgery decreased from 9.5 to 9.0 (p = 0.154). In three of 30 preoperatively IOP regulated eyes the postoperative IOP was 21 mm Hg. The control group showed an average IOP decrease of 2.01 mm Hg (p = 0.014) 12 months after cataract surgery.

Conclusion: An increase in IOP was found 1 year after phacoemulsification in half of the filtered glaucomatous eyes. IOP in glaucomatous eyes without previous filtering surgery decreased in the same period. Cataract extraction using clear cornea phacoemulsification may be associated with a partial loss of the previously functioning filter and with an impairment of filtering bleb morphology.

Cataract formation may be accelerated by filtering surgery especially in eyes with postoperative hypotony, flat anterior chamber, or excessive inflammation. It has been reported that cataract surgery can compromise the function of the filtering bleb, resulting in loss of intraocular pressure (IOP) control. In a number of retrospective studies a rise of IOP after extracapsular cataract extraction and even after phacoemulsification in filtered glaucoma eyes was shown.

Our goal was to prospectively investigate the influence of clear cornea phacoemulsification on filtering bleb morphology, function and intraocular pressure in glaucoma eyes with previously successful filtering surgery.

METHODS

A prospective and controlled study was designed to include 66 eyes of 66 patients with chronic open angle (high pressure) glaucoma and visual acuity limiting cataract before phacoemulsification. Thirty patients had previously undergone a successful glaucoma filtering surgery with controlled IOP <21 mm Hg (bleb group), when additional glaucoma medication was allowed. Thirty six patients with open angle glaucoma controlled by medication had had no glaucoma surgery before (control group). We included one eye of each patient. Patients with low tension glaucoma and angle closure glaucoma were excluded.

Ophthalmological examination consisted of best corrected visual acuity, Goldmann applanation tonometry at least three measurements distributed over daytime, a detailed slit lamp examination of the filtering bleb using standardised criteria, and filtering bleb photography. The following morphological criteria were evaluated: vascularisation, corkscrew vessels, microcysts, encapsulation, and bleb elevation (table 1). We created a score (0–12) for a semiquantitative analysis of the bleb. A high bleb score (12 = optimum) indicates a “favourable,” functioning filtering bleb. The bleb elevation was calculated separately using equivalents of corneal thickness for quantification. Patients were examined before phacoemulsification, between the first and fourth postoperative day, 6 months, and 12 months postoperatively.

Cataract surgery was performed by three surgeons (FG, JS, WL) by phacoemulsification via temporal clear cornea incision with implantation of a foldable lens (Acrysof IOL Model MA60BM, Rayner Model 574R, and Memory lens IOL Model U940A) into the capsular bag.

Statistical analysis

The Wilcoxon test was used for longitudinal comparison of intra-individual IOPs, visual acuity, number of glaucoma medications, and changes in bleb morphology. Linear regression analysis was performed to investigate the influence of the interval between glaucoma and cataract surgery on IOP outcome and the relation between IOP and bleb score. Comparisons between bleb and control group were performed by using Mann-Whitney U test, Meta/Patel, test and contingency table. A p value of 0.05 or less was considered statistically significant.

StatView (SAS Institute Inc, USA) and MEDAS (Grund Company EDV-Systems, Germany) were used for statistical analysis.

RESULTS (TABLE 2)

Bleb group

The mean IOP of the filtering bleb group increased after phacoemulsification by 2.05 (SD 4.2) mm Hg within 1 year (preoperatively 14.28 (3.71) mm Hg, 1-4 days postoperatively 15.93 (2.68) mm Hg, 6 months postoperatively 15.73 (4.12) mm Hg, 12 months postoperatively 16.33 (3.31) mm Hg, p = 0.0057, fig 1 and fig 3).
In 15 patients (50%) the IOP increased by >2 mm Hg, 11 patients (36.7%) had no IOP difference (SD 2 mm Hg), and in four patients (13.3%) IOP decreased >2 mm Hg within 1 year.

In three of 30 preoperatively IOP regulated eyes the postoperative IOP was >21 mm Hg.

One patient required cyclophotocoagulation 9 months after phacoemulsification because of a persistent IOP increase. There was no significant difference of IOP outcome between patients who received antimetabolites during or after glaucoma surgery and those who did not. The IOP before phacoemulsification in patients who previously had glaucoma surgery with antimetabolites (n = 6) was 14.0 (3.4) mm Hg and 17.3 (4.2) mm Hg after 12 months. The IOP before phacoemulsification in patients who previously had glaucoma surgery without antimetabolites (n = 24) was 14.3 (3.8) mm Hg and 16.1 (3.1) mm Hg after 12 months (p = 0.22).

There was no significant correlation between the IOP change and the time between glaucoma and cataract surgery (preoperative versus 12 months after cataract surgery, calculated with linear regression analysis, $R^2 = 0.002$, p = 0.806 ANOVA).

### Control group

The control group showed an average IOP decrease of 2.01 mm Hg (p = 0.014) 12 months after cataract surgery. The mean IOP before surgery was 17.59 (5.26) mm Hg, 17.63 (5.02) mm Hg on the first postoperative day, 14.58 (3.17) mm Hg on the second postoperative day, 15.71 (2.19) mm Hg 6 months postoperatively, and 15.58 (3.15) mm Hg 12 months postoperatively (figs 2 and 4).

13 Patients (36.1%) showed an IOP decrease of more than 2 mm Hg within 1 year, 17 patients (47.2%) had no IOP difference and six patients (16.7%) had an IOP increase of >2 mm Hg. In one patient the IOP was not controlled.

### Table 1 Standardised filtering bleb classification and bleb score

<table>
<thead>
<tr>
<th>Vascularisation</th>
<th>Classification</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = avascular</td>
<td>0, 0–1</td>
<td>3</td>
</tr>
<tr>
<td>1 = equal to surrounding conjunctiva</td>
<td>1, 1–2</td>
<td>2</td>
</tr>
<tr>
<td>2 = enhanced</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3 = massive</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screw vessels</th>
<th>Classification</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = no</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1 = in 1 third</td>
<td>0–1</td>
<td>2</td>
</tr>
<tr>
<td>2 = in 2 third parts</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3 = in whole bleb</td>
<td>2, 3</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microcyts</th>
<th>Classification</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = no</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 = above scleral flap</td>
<td>0–1, 1</td>
<td>1</td>
</tr>
<tr>
<td>2 = at one side</td>
<td>1–2, 2</td>
<td>2</td>
</tr>
<tr>
<td>3 = in whole bleb</td>
<td>2–3, 3</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Encapsulation</th>
<th>Classification</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = no</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1 = in 1 third</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2 = in 2 third parts</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3 = in whole bleb</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 2 Demographic data, glaucoma diagnosis, additional interventions, and complications

<table>
<thead>
<tr>
<th></th>
<th>Bleb group</th>
<th>Control group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/eyes</td>
<td>30</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>17/13</td>
<td>21/15</td>
<td>0.86 (A)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>70.6 (8.5)</td>
<td>76.2 (6.8)</td>
<td>0.19 (B)</td>
</tr>
<tr>
<td>Range</td>
<td>49.7–84.5</td>
<td>57.3–86.1</td>
<td></td>
</tr>
<tr>
<td>Glaucoma diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary open angle glaucoma</td>
<td>22 (73%)</td>
<td>26 (72%)</td>
<td>0.82 (A)</td>
</tr>
<tr>
<td>Pseudoxfoliation</td>
<td>7 (23%)</td>
<td>10 (28%)</td>
<td></td>
</tr>
<tr>
<td>Secondary glaucoma</td>
<td>1 (3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Glaucoma surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trabeculectomy (Cairns)</td>
<td>24 (80%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With antimetabolites</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitomycin C (intraoperatively)</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil (intraoperatively)</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil (postoperatively)</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Goniotriphination (without antimetabolites)</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Time between glaucoma surgery and phaco</td>
<td>5.8 (6.2) years</td>
<td>3 months–19.7 years</td>
<td></td>
</tr>
<tr>
<td>Phacoemulsification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional manipulation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synchelolysis</td>
<td>15</td>
<td>10</td>
<td>0.14 (A)</td>
</tr>
<tr>
<td>Iris retractors</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Capsule tension ring</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Intraoperative complication:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior capsular tear with vitreous loss</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Zonulolysis</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Postoperative complication:</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Fibrin reaction</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

A = Meta/Patel test.
B = Mann-Whitney U test.
The difference in IOP changes of bleb group and control-group (table 3) is statistically significant (p = 0.0089).

**Glaucoma medication**

The mean number of glaucoma medications (0.8 before cataract surgery, 0.7 immediately postoperatively, 0.7 at 6 months postoperatively, 0.7 at 12 months postoperatively) did not change significantly during the 12 months follow up period. The number of patients in the bleb group who did not require any glaucoma medication after phacoemulsification decreased from 67% before to 57% at 12 months.

**Bleb morphology**

Figure 5 shows the correlation between IOP changes and bleb morphology, which indicates no strong linear relation ($R^2 = 0.588$, p = 0.233).

The mean score of filtering bleb morphology 1 year after surgery decreased from 9.5 (2.8) points to 8.9 (3.4) points (p = 0.154) (table 4). The number of corkscrew vessels and general vascularisation significantly increased in the first days after cataract surgery (p = 0.027) (fig 6). The tendency of encapsulation remained stable over 12 months. The elevation of the filtering bleb significantly decreased from 1.6 (1.1) to 1.0 (0.6) corneal thickness equivalents (p = 0.0013).

**Visual acuity**

Visual acuity improved significantly after phacoemulsification from an average of 0.14 (5.5) lines (0.85 logMAR) before surgery to 0.43 (3.6) lines (0.37 logMAR) 12 months later (p = 0.0001). Twenty nine eyes (96.7%) had a better visual acuity after phacoemulsification, one eye lost two lines of visual acuity because of epiretinal gliosis. 19 eyes (63.3%) achieved a final best corrected visual acuity of 0.5 or better.

**DISCUSSION**

As glaucoma requires a lifelong management, the development of cataract is a significant concern because its treatment may lead to loss of IOP control. There are differing reports on IOP changes after cataract surgery in glaucoma filtered eyes, ranging from a decrease of 0.8 mm Hg to an increase of 6.6 mm Hg (follow up ranging from 8 to 70 months). In our prospective, controlled study we found a statistically significant mean IOP increase of 2.05 mm Hg 1 year after phacoemulsification (p = 0.0057). To our knowledge there are only two prospective studies on this topic. In a comparable prospective study, Rebolleda and Munoz-Negetre reported similar results with a mean IOP increase of 2.04 mm Hg 12 months after phacoemulsification (p = 0.0057). To our knowledge there are only two prospective studies on this topic.

In a comparable prospective study, Rebolleda and Munoz-Negetre reported similar results with a mean IOP increase of 2.04 mm Hg 12 months after phacoemulsification. Khokar et al found no statistically significant IOP difference before and after phacoemulsification. In this study only chronic angle closure glaucoma eyes were included and IOP control was achieved by lens extraction in up to 68% as a result of anterior chamber deepening. In our study we excluded eyes with angle closure glaucoma to avoid opposite mechanisms of action in different forms of glaucoma.

There is a number of retrospective studies showing an IOP increase after cataract surgery (ECCE or phaco) in filtered glaucoma eyes, few authors reported on IOP.
**Table 3** Intraocular pressure (IOP) changes after phacoemulsification in bleb group versus control group

<table>
<thead>
<tr>
<th></th>
<th>Bleb group</th>
<th>Control group</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP increase &gt;2 mm Hg</td>
<td>15</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>no IOP change</td>
<td>11</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>IOP decrease &gt;2 mm Hg</td>
<td>4</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Totals</td>
<td>30</td>
<td>36</td>
<td>66</td>
</tr>
</tbody>
</table>

χ², p value 0.0089.

In our study we matched a control group with respect to age, sex, IOP, glaucoma diagnosis, and duration of follow up to compare our results after phacoemulsification to those without previous glaucoma surgery. This control group showed a mean IOP decrease of 2.01 mm Hg (p = 0.0014) in the 12 months follow up. 36% of the patients of the control group had an IOP decrease of ≥2 mm Hg. This corresponds well with previously published data.

For interpretation IOP regulation in filtered eyes we have to consider the normal course of IOP after filtering surgery. In the Advanced Glaucoma Intervention Study (AGIS) an average IOP increase at the 72 months follow up (corresponding to our interval) was measured: 0.33 mm Hg IOP increase (<14 mm Hg group), 1.11 mm Hg IOP increase (14–17.7 mm Hg group), 2.60 mm Hg IOP increase (>17.5 mm Hg group). These data show that a slight increase of IOP over time is common after trabeculectomy. Therefore the influence of phacoemulsification on IOP may not as high as it seems to be.

In contrast with Chen et al we did not find an influence of the glaucoma diagnosis or of any intraoperative manipulation (for example, iris retractors) on IOP. Furthermore, we could not demonstrate an effect of antimetabolites used during glaucoma surgery on the IOP outcome or filtering bleb morphology, but only six patients received antimetabolites.

Also there was no influence of the interval between glaucoma and cataract surgery on IOP outcome (R² = 0.002, p = 0.806).

It was a major concern of this study to find a correlation between filtering bleb development and IOP using well defined morphological slit lamp criteria. Most reports in the literature only focused on bleb size, elevation, vascularisation, and vascularity. To our knowledge a detailed and standardised definition of morphological slit lamp criteria (table 1) increased vascularisation might accelerate the migration of inflammatory cells and fibroblasts resulting in collagen formation. Contraction of collagen fibrils leads to the development of corkscrew vessels, while microcysts are a sign of good filtration of the bleb. The investigator has to pay attention on corkscrew vessels and encapsulation as signs of imminent scar formation.

A modification of our bleb classification has recently been used in a prospective study to investigate the morphological appearance of filtering blebs after primary MMC trabeculectomy.

We used four criteria (vascularisation, corkscrew vessels, microcysts and encapsulation) to establish a semiquantitative score. The mean bleb score decreased from 9.5 points before phacoemulsification to 8.9 points after 1 year which was not statistically significant (p = 0.154). However, in some specific parameters some interesting changes were noticed. The follow up immediately after phacoemulsification revealed an increase in vascularisation and corkscrew vessels according to the surgical trauma (see fig 6). Encapsulation remained stable over 1 year follow up. Elevation was not included in our bleb score, because it might have favourable (good filtration) and also unfavourable aspects (prominent Tenon cyst). We calculated the bleb elevation separately using corneal thickness equivalents for quantification. The mean elevation significantly decreased from 1.6 (1.1) to 1.0 (0.6) corneal thickness equivalents (p = 0.0013). This is comparable to previously published results, which described a reduction in bleb size and elevation. The reason for the decrease of elevation might be a transient reduced production of aqueous humour followed by a decreased flow through the trabeculectomy resulting in bleb flattening. Although we could not find a strong linear relation between IOP outcome and bleb score (fig 6), the tendency that a higher IOP and a more “unfavourable” filtering bleb are related is obvious.

Thirty three per cent of the filtering blebs were classified as “favourable” (≥10 points) before phacoemulsification, 27%

---

**Figure 5** Mean intraocular pressure (A) versus mean bleb morphology score (B). *Significant p<0.05.

**Figure 6** Mean score of individual filtering bleb parameters.
remained “favourable” at the 12 month visit. Hence, there was only little general effect of phacoemulsification on bleb morphology as detectable with slit lamp biomicroscopy. Although there are only few long term changes in bleb morphology, a standardised bleb evaluation is very important in the early postoperative period after trabeculectomy to be always aware of early signs of bleb scarring.

Our results indicate that a phacoemulsification may jeopardise a previously functioning filtering bleb, resulting in IOP increase. In this respect, the cataractogenesis of glaucoma surgery may become an important issue for indication of both glaucoma and cataract surgery.

---

**Table 4** Bleb morphology score of filtered eyes before and after phacoemulsification

<table>
<thead>
<tr>
<th></th>
<th>Before phaco</th>
<th>1st–4th postop day</th>
<th>6 months postop</th>
<th>12 months postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean score</td>
<td>9.5</td>
<td>8.7</td>
<td>9.3</td>
<td>8.9</td>
</tr>
<tr>
<td>SD</td>
<td>2.8</td>
<td>3.0</td>
<td>3.0</td>
<td>3.4</td>
</tr>
<tr>
<td>p Value</td>
<td>0.0214*</td>
<td>0.935</td>
<td>0.54</td>
<td>0.154</td>
</tr>
<tr>
<td>Total appearance of filtering bleb (max 12 points)</td>
<td>17%</td>
<td>21%</td>
<td>24%</td>
<td>15%</td>
</tr>
</tbody>
</table>

**Statistical significant (Wilcoxon test).**

---

**REFERENCES**

EXTENDED REPORT

The origins of polypoidal choroidal vasculopathy

M Yuzawa, R Mori, A Kawamura

Background/aim: There are two theories on the pathogenesis of polypoidal choroidal vasculopathy (PCV): variants in choroidal neovascularisation (CNV) and inner choroidal vessel abnormalities. On indocyanine green angiography (IGA) with a video camera system, PCV has a characteristic appearance, but inadequate image quality has made detailed interpretation difficult. This study aims to improve imaging, using confocal scanning laser ophthalmoscopy (SLO), to elucidate the pathogenesis of PCV.

Methods: High speed IGA with confocal SLO of 45 eyes (44 patients) showed typical PCV findings of a branching vascular network and polypoidal lesions.

Results: Vessels comprising branching networks began to fill simultaneously with the surrounding choroidal arteries in 38 eyes. Small numbers of vessels filling within a branching network, in the arterial and arteriovenous phases of IGA, showed focal dilatation, constriction, and tortuosity. Vessel abnormalities, corresponding to polypoidal lesions, existed within a network in eight eyes and included loops similar in calibre to network vessels, and numerous microaneurysmal dilatations of small vessels. Vessel pulsation was seen in 24 eyes.

Conclusion: PCV is caused by inner choroidal vessel abnormalities, not CNV.

SUBJECTS AND METHODS

We examined 45 eyes (44 patients; 40 males, four females, average age 65 years, range 53–81 years) with typical PCV features—that is, serous and haemorrhagic detachments of the RPE and/or neurosensory retina. Other major features were branching vascular networks and polypoidal lesions in the posterior pole, on IGA with confocal SLO (Heidelberg retina angiograph, Heidelberg Engineering, Germany). Eyes also showing classic choroidal neovascularisation (CNV) were excluded.

The 45 eyes underwent fundus photography, fluorescein angiography and IGA. For IGA, indocyanine green dye (25 mg in 1 ml balanced saline) was injected into the cubital vein. IGA images were obtained for the initial 20 seconds, then at intervals, until 30 minutes had elapsed. We assessed when network vessels began to fill, their filling state, and the mechanisms of hypofluorescence in early and hyperfluorescence in late phase IGA, in and around network vessels. We observed the locations, architecture, and late phase IGA conditions of polypoidal lesions. Pulsation in branching vessels and/or polypoidal lesions was also determined.

RESULTS

In all 45 eyes, IGA showed arteries of branching vascular networks to overlie large choroidal vessels. These arteries began to fill simultaneously with the surrounding choroidal arteries in 38 eyes. Filling of individual arteries could not be confirmed in seven eyes because of small vessel calibre, rapid dye filling, or blocked fluorescence in part of the network, as a result of RPE detachment or haemorrhage. In 30 eyes, the area within and adjacent to the surrounding network hypofluoresced, in both the arterial and arteriovenous phases of IGA, because of vessel paucity (figs 1A, 2A, 3A). Vessels comprising networks varied in size (figs 1–6) and showed focal dilatation, constriction (figs 2, 3), tortuosity (figs 2–5), and unusual courses (figs 2–5). Filling was slow in 20 eyes (fig 3).

The area of hypofluorescence including the network and immediately adjacent areas changed to hyperfluorescence late in IGA (figs 2D, 6B) in 37 eyes but was similar to that in the surrounding area in eight. Hyperfluorescence existed above the network, indicating leakage from network vessels, in 26 of 30 eyes examined stereoscopically.

Polypoidal lesions were at the network border in all 45 eyes, but also within it in eight (fig 7). The internal IGA findings of polypoidal lesions were classified into: (1) dense clusters of numerous small hyperfluorescent dots resembling microaneurysmal dilatations (fig 8A); (2) polypoidal lesion consisting of relatively large aneurysmal dilatations, occasionally resembling grape clusters (fig 8B); (3) characteristic large vessel deformations—for example, loop or coil-like configurations, constrictions, and dilatations (fig 8C). The calibre of vessels with unusual configurations is sometimes similar to that of network vessels (fig 2). Uniform or

Abbreviations: AMD, age related macular degeneration; CNV, choroidal neovascularisation; IGA, indocyanine green angiography; OCT, optical coherence tomography; PCV, polypoidal choroidal vasculopathy; RPE, retinal pigment epithelium; SLO, scanning laser ophthalmoscopy.
non-uniform hyperfluorescence late in IGA, corresponding to most polypoidal lesions, was attributed to leakage from focal or global abnormalities of vessels entering polypoidal lesions (fig 9). Ring of hyperfluorescence (18 eyes) was attributed to looped vessel leakage at the polypoidal lesion base (fig 10).

Pulsation was detected in 24 eyes; in only network vessels in 14, in only polypoidal lesions in five, and in both in five.

**DISCUSSION**

PCV pathogenesis remains controversial. One proposed mechanism involves CNV, another development of choroidal vasculature abnormalities. We examined the possible contributions of both mechanisms to PCV.

Yanuzzi et al noted that late phase staining characteristic of CNV was not seen in PCV vascular lesions and concluded that branching vascular networks with bordering polypoidal lesions are unique to PCV. Moorthy et al concluded that dilated PCV vessels arise from the choroidal vasculature rather than classic CNV. Yanuzzi et al also described PCV as a primary abnormality of the choroid.

PCV is not rare in Japan. As biomicroscopy and ophthalmoscopy indicated PCV vascular abnormalities to lie between the RPE and Bruch's membrane, Uyama et al concluded that in Japanese patients PCV is a peculiar form of CNV. They described lesions termed polypoidal CNV. Tateiwa et al described a large vessel variant, expanding across the vascular arcade, in 12 (20%) eyes in a PCV series. The dilated vessel network spread radially. Six eyes had subretinal CNV. This large vessel variant appeared to represent CNV, with a worse prognosis than smaller PCV lesions. In a study of 110 PCV eyes, Sho et al noted slow progression of vascular abnormalities and little subretinal fibrovascular proliferation, indicating that PCV has little association with classic CNV.

Otsuji et al used optical coherence tomography (OCT) to study PCV. OCT did not reveal branching vascular network origins, indicating that abnormal vessels in PCV are due to...
CNV with polypoidal vascular dilatations. They consider PCV to be a type of age related macular degeneration (AMD) with peculiar vascular formations. Iijima et al., using OCT on two PCV eyes, observed polypoidal structures protruding from the inner choroid and speculated that these lesions cause serosanguineous RPE detachments via damage to the overlying Bruch’s membrane and/or RPE, and even adhesion between the two.\textsuperscript{16}

Studying two macular translocation specimens using a light microscope, Terasaki et al identified a fibrovascular membrane within Bruch’s membrane in one eye with PCV.\textsuperscript{17} Clusters of thin walled dilated vessels correlated with polypoidal structures on ophthalmoscopy and IGA, indicating that the fibrovascular complex was subretinal CNV. However, this eye had previously undergone radiation for a subretinal neovascular membrane, making radiation associated choroidal neovasculopathy a possibility.\textsuperscript{18}

A fibrovascular sub-RPE lesion described by Lafaut et al was also within Bruch’s membrane but beneath the diffuse drusen, contained inflammatory cells and dilated, thin walled vessels, some with very large lumens, suggesting PCV to represent an AMD variant.\textsuperscript{19} The reliability of surgical specimen studies is often limited by disease severity and/or coexisting disorders.\textsuperscript{19–21} Secondary histopathological changes cannot be ruled out.

Sub-RPE and intra-Bruch’s membrane choroidal neovascularisation was shown in the peripapillary lesion of an enucleated eye because of angle closure glaucoma.\textsuperscript{22} Okubo et al used light and electron microscopy, on a surgically excised macular PCV lesion, to identify a degenerated RPE-Bruch’s membrane-choriocapillaris complex.\textsuperscript{23} An unusually dilated, tortuous venule adjacent to a sclerotic arteriole and two native inner choroid vessels appearing to form an arteriovenous crossing, suggested hyperpermeability, haemorrhage, and sclerosis, at the crossing site, to promote oedema and tissue degeneration. Histopathological similarities with branched vein retinal occlusion were noted. A venule with stasis might become fragile, leading to the beaded or polypoidal configurations of PCV. Vessel pulsation suggested arterial involvement. These findings suggest PCV polypoidal lesions to be inner choroidal vasculature abnormalities.

High speed video IGA with confocal SLO is useful for investigating early vessel filling because high speed images with enhanced contrast show fluid dynamics clearly. With diminished light scattering, detailed internal polypoidal lesion architecture is visualised. We showed network vessel filling begins simultaneously with that of adjacent choroidal arteries. Branching vessels do not represent CNV, based on observation of polypoidal lesions within branching vascular networks. Vessels within networks had tortuous courses, often with constriction and dilatation. Arteries and veins took unusual courses, apparently as a result of disappearing and anastomosing with other vessels. Our findings mirror Yanuzzi et al’s who noted marked morphological variability in abnormal vessels of PCV.\textsuperscript{24}

\begin{figure}[h]
\centering
\includegraphics[width=\linewidth]{figure3}
\caption{Indocyanine green angiography. Few hyperfluorescent vessels are surrounded by hypofluorescence (arrow). Area in and around arteries hypofluoresces because of vessel paucity (A, 23 seconds). Vessel, with constriction and dilatation, filled slowly (arrow) (B, 29 seconds). Dilatation is more prominent (arrows) (C, 32 seconds).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\linewidth]{figure4}
\caption{Indocyanine green angiography. Vessels with abnormal courses appear to be arteries (arrows) (A, 17 seconds), other vessels veins (B, 28 seconds).}
\end{figure}
Pulsation, seen in normal and shunt vessels, is not a feature of CNV, instead indicating arterial involvement and increased intravascular pressure. Pulsation suggests branching network vessels arising from the inner choroidal vasculature. Vessels persisting in networks showed focal dilatation, constriction, and tortuosity. Slow filling early in and dye leakage late in IGA indicated stasis and exudation from branching network vessels. However, there was no late phase hyperfluorescence in eight eyes—that is, leakage from network vessels stops in some cases. Although this probably involves mature vessels, differences between networks with and without hyperfluorescence merit further study.

We observed marked differences in vessel calibre among patients. Yanuzzi et al reported the portion of the choroidal vasculature evolving into PCV networks to vary among patients, indicating network vessels to lie at various levels within the choroid.

Polypoidal lesions also presented a spectrum of abnormalities and involved different sized vessels. Clusters of microaneurysmal hyperfluorescent dots indicate small deformed vessels. Polypoidal lesions, apparently resulting from build ups of large deformed vessels, comprised dilated portions of larger tortuous venules. Unusual configurations
**Figure 8** (A–C) Internal polypoidal lesion structure.

**Figure 9** Internal polypoidal lesion structure. Two large vessels, within a polypoidal lesion, show dilatation and constriction. Small vessels apparently form bridge between the two large vessels (A, 14 seconds). Dye leaked from dilated portions of large vessels (B, 27 seconds) accumulates in upper half of the polypoidal lesion (C, 208 seconds).

**Figure 10** Four months after fundus photographs in figure 9. Indocyanine green angiography shows disappearance of small bridging vessels (A, 33 seconds); Leakage from dilated portions of looped vessels (B, 35 seconds); consists of ring of hyperfluorescence (C, 1680 seconds).
of vessels the same size as those in branching networks included vascular loops and bead strings. None of our polypoidal lesions showed dilatations at termini of branching network vessels. Like Iijima et al., we observed, ophthalmoscopically, reddish orange lesions—that is, polypoidal lesions apparently resulting from serosanguineous RPE detachment caused by exudation from dilated abnormal vessels protruding from the inner choroid.

Lesions with hypofluorescent cores and surrounding hyperfluorescent walls, late in IGA, represent rings of hyperfluorescence.2 Spaide considered dye initially collecting in the polypoidal lesion core and then becoming relatively hypofluorescent with a surrounding hyperfluorescent ring late in IGA, to represent polypoidal lesions resulting from terminal expansion of branching network vessels.2 Kwok et al described the lesion core as becoming hypofluorescent with washout of dye producing a ring silhouette of stained polyps.25 We attributed this finding to morphological abnormalities of polypoidal lesion vessels. As dye intensity fades, leakage from a looped vessel becomes visible as a ring of hyperfluorescence.2

Our observations of eyes with typical features suggest that inner choroidal vessel abnormalities may be the pathogenesis of PCV. Taken together, our results and others suggest that PCV is classifiable into three groups. The most common type involves choroidal vasculature abnormalities, in the present narrow sense. A second type is polypoidal CNV, expanding rapidly under the RPE, ultimately with polypoidal lesions developing at vessel termini. Radiation associated choroidal neovasculopathy is the third type.

Authors’ affiliations
M Yuzawa, R Mori, A Kawamura, Surugadai Hospital, Nihon University, 1-8-13 Surugadai, Kanda, Chiyoda-ku, Tokyo, Japan

REFERENCES
ANCA associated pauci-immune retinal vasculitis

M J Gallagher, K G-J Ooi, M Thomas, M Gavin

Background: Antineutrophil cytoplasmic antibodies (ANCA) are useful diagnostic serological markers for the most common forms of necrotising vasculitis. ANCA associated vasculitides represent distinctive clinicopathological categories—for example, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, and idiopathic necrotising crescentic glomerulonephritis, collectively known as the small vessel pauci-immune vasculitides.

Method: Three cases of ANCA associated pauci-immune retinal vasculitis are described. Their systemic features are described and the clinical significance of ANCA as a diagnostic test in relation to retinal vasculitis discussed.

Results: These three cases represent a spectrum of clinical features associated with retinal vasculitis. Two cases have evolved into clinical recognisable entities as microscopic polyangiitis. Adherence to the international consensus statement on testing and reporting of ANCA is recommended and the authors speculate that the incidence of microscopic polyangiitis may be underestimated because of the under-recognition of systemic involvement in patients with retinal vasculitis.

Conclusion: The receipt of a positive ANCA result should always raise the suspicion of a pauci-immune systemic vasculitis and prompt appropriate investigation. The authors emphasise the importance of the evaluation of systemic features in these patients with retinal vasculitis, enabling earlier recognition and thereby preventing significant morbidity and mortality.

CASE REPORTS

Case 1

A 35 year old woman presented with pain and blurring of vision in her right eye. She related systemic complaints of malaise, lethargy, weight loss, and intermittent night sweats. Blood pressure was normal, urinalysis demonstrating moderate haem ++.

Examination demonstrated a right visual acuity of 3/60 (improving to 6/9 with pinhole). There were cells+ in the anterior chamber, the posterior segment demonstrating vitreous cells+++ Fundoscopy revealed peripheral vascular sheathing (fig 1).

Blood results revealed a positive P-ANCA on immuno-fluorescence (MPO/PR3 testing not available at this time) with an elevated erythrocyte sedimentation rate (94 mm in the first hour), and C reactive protein (20 mg/l). Serum antinuclear antibody testing was intermittently positive at 1:40 (on Hep2000 cells). Investigations for retinal vasculitis—namely, full blood count, urea and electrolytes, liver function tests, serum angiotensin converting enzyme, complement, rheumatoid factor, HLA B-27, serum VDRL, anti-cardiolipin antibodies, and a chest radiograph were normal.

The patient was treated conservatively with topical corticosteroids. Further exacerbations, resulted in bilateral ocular involvement with extensive peripheral retinal vasculitis (fig 2). Symptoms included fatigue, lethargy, arthralgia, weight loss, and loin pain. Systemic examination demonstrated finger pulp haemorrhages indicative of cutaneous vasculitis.

Renal ultrasound was normal. Repeat urinalysis demonstrated persistent haematuria. Serial mid-stream urine specimens were negative demonstrating no evidence of pus cells or organisms. A renal biopsy demonstrated an interstitial lymphocytic infiltrate with absence of immune complex deposition indicative of glomerulonephritis (fig 3).

Figure 1 Peripheral retinal vasculitis with vascular sheathing.

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; MPO, myeloperoxidase
function was normal. P-ANCA was persistently positive but was negative for MPO and PR3 antibodies. Serum antinuclear antibody (ANA) was intermittently positive (low titre). Serum ANA, however, was negative when serum ANCA was at its strongest titre (1:640) suggesting that she did indeed have a positive ANCA (fig 4).

The patient responded favourably to systemic steroid treatment with adjunctive cyclosporin (150 mg twice daily). Further monitoring demonstrated a decline in renal function with an isotope glomerular filtration rate of 63 ml per minute with normal serum urea and creatinine levels. Cyclosporin therapy was discontinued and mycophenolate mofetil (1 g twice daily) commenced to continue immunosuppression which has protected against further renal compromise.

**Case 2**

A 39 year old woman presented with a painless reduction of vision in her left eye. She related paraesthesia in both her legs over the previous few months. Blood pressure was 160/100 mm Hg, with normal urinalysis.

Examination of her left posterior segment demonstrated a vitreal haemorrhage with neovascularisation in the left superotemporal quadrant. The right posterior segment also demonstrated active retinal vasculitis. A vasculitic screen was performed.

Serum P-ANCA was positive with a 1:20 titre. Anti-MPO and PR3 antibodies were negative. Serum ANA was negative. Routine bloods were normal. C reactive protein was mildly elevated at 21 mg/L, with a normal erythrocyte sedimentation rate. Computed tomography (CT), brain, and electroencephalogram (EEG) measurements were normal. There were no other neurological symptoms to suggest multiple sclerosis. A clinical diagnosis of presumed mononeuritis multiplex was made with no cause elucidated.

She underwent a sectoral panretinal photocoagulation and was commenced on cyclosporin therapy (100 mg twice daily) to which she responded well with quiescence of her retinal vasculitis.

**Case 3**

A 28 year old woman presented with a reduction in vision in her left eye. Blood pressure was 115/84 mm Hg with normal urinalysis.

Examination demonstrated a left visual acuity of hand movements, a quiet anterior chamber with evidence of posterior segment vitreal haemorrhage. On resolution of the vitreal haemorrhage over a 7 week period, further re-examination demonstrated vitreal cells++ with peripheral retinal vasculitis and a localised area of neovascularisation inferiorly. Investigation of this patient’s retinal vasculitis demonstrated a positive P-ANCA (1:160) on immunofluorescence, which was negative for anti-MPO and PR3 antibodies. Serum ANA was negative. Routine bloods and renal function were normal.

This patient presented with pauci-immune retinal vasculitis without systemic involvement. She was commenced on cyclosporin (125 mg twice daily) (patient was reluctant to commence steroid treatment) and responded well, with quiescence of the vasculitis, an improvement in visual acuity to 6/9 left eye, with no further episodes of vitreal haemorrhage.

**DISCUSSION**

These cases represent a spectrum of clinical features associated with retinal vasculitis. The first case presented with a chronic history of arthralgia, followed by systemic features of fatigue, lethargy, weight loss, mononeuritis multiplex, finger pulp haemorrhages, and loin pain.

Our patient developed a progressive deterioration in glomerular filtration rate, indicative of intrinsic renal disease. No immune complex deposition was seen on renal biopsy. In conjunction with a positive P-ANCA and in the absence of granulomatous inflammation or the presence of eosinophilia or asthma in this patient, a diagnosis of microscopic polyangiitis was made.

It is highly probable that our second case is also a case of evolving MPA (according to the international consensus statement) presenting with bilateral retinal vasculitis and peripheral neuropathy in association with a positive P-ANCA. Our third P-ANCA positive retinal vasculitis case continues to be screened for associated systemic features. Our paper describes three cases of retinal vasculitis, all with positive serum P-ANCA, two of which have evolved into clinically recognisable entities as MPA. Jennette et al suggest that patients who initially have clinical manifestations consistent
with MPA may subsequently develop features of Wegener’s granulomatosis.  

These patients presented with retinal vasculitis in association with a positive P-ANCA on immunofluorescence, negative for anti-MPO and PR3 antibodies. Despite the absence of either MPO or PR3 antibodies two of our patients showed evidence of systemic vasculitic involvement. We suggest that any patient with P-ANCA positivity (by ELISA or indirect immunofluorescence) and retinal vasculitis, regardless of specificity should be reviewed for evidence of systemic vasculitis. When systemic clinical features are present the demonstration of ANCA is probably 95% sensitive and 90% specific for these diseases and has a much higher positive predictive value than in other hospitalised patients.  

In an attempt to clarify the testing and reporting of ANCA serology, an international consensus statement was formulated. The consensus recommends testing for ANCA in patients with:

- glomerulonephritis
- pulmonary haemorrhage
- cutaneous vasculitis with systemic features
- mononeuropathy or other peripheral neuropathy
- longstanding sinusitis or otitis
- subglottic tracheal stenosis
- retro-orbital mass.

The presence of one of these clinical features, or other strong clinical evidence for small vessel vasculitis with a positive ANCA test provides 90% confirmation of pauci-immune small vessel vasculitis with a negative result does not rule out this category of vasculitides. AANCA points towards different clinicopathological phenotypes of the small vessel pauci-immune vasculitides. A negative result does not rule out this category of vasculitides (table 1).  

Microscopic polyangiitis is a now recognised pauci-immune systemic vasculitis. Small vessel involvement is the definitive diagnostic criterion of MPA and excludes the diagnosis of polyarteritis nodosa even if medium sized arterial lesions are also seen. MPA has an incidence of approximately 1:100 000 with a slight female predominance, a mean age of onset of 50 years, although any age may be affected.  

The pathophysiological relevance of ANCA has been studied extensively. It has been demonstrated that IgG fractions from ANCA positive sera, are capable of inducing tumour necrosis factor primed neutrophils to release lysosomal enzymes and produce reactive oxygen species inducing vascular injury. ANCA associated vasculitides are described as being pauci-immune, characterised by necrotising inflammation but with a paucity of immune deposits.  

The recommended treatment for MPA is high dose corticosteroids and cyclophosphamide. Dandekar et al, in their recent series on ocular involvement in systemic vasculitis, relate that treatment with immunosuppressants resulted in a reduction in P-ANCA titre with dramatic improvement of symptoms.  

In conclusion, we advocate the testing of all patients with retinal vasculitis for serum ANCA. We acknowledge that ANCA specificity does not allow us to distinguish diverse forms of necrotising vasculitis. We speculate that the incidence of MPA may be underestimated because of the under-recognition of systemic involvement in patients with retinal vasculitis. We emphasise the importance in this regard of recognition of these clinical features and the differential diagnosis of these pauci-immune small vessel vasculitides so that prompt immunosuppressive therapy is instituted and patient morbidity, if not mortality, is prevented.

ACKNOWLEDGEMENTS

We thank the library staff and Medical Illustration Department at Gartnavel General Hospital, Glasgow.

Authors’ affiliations
M J Gallagher, K Ooi, M Gavin, Tennent Institute of Ophthalmology, Gartnavel General Hospital, Glasgow, UK
M Thomas, Department of Immunology, Western Infirmary, Glasgow G11, UK

REFERENCES


Table 1  Serum ANCA specificity in untreated disease

<table>
<thead>
<tr>
<th></th>
<th>PR3-ANCA</th>
<th>MPO-ANCA</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic polyangiitis</td>
<td>40%</td>
<td>50%</td>
<td>10%</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>75%</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>10%</td>
<td>60%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Adapted from Jennette et al.

Table 2  Clinical manifestations of microscopic polyangiitis

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal manifestations</td>
<td>78.8%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>72.9%</td>
</tr>
<tr>
<td>Skin involvement</td>
<td>62.4%</td>
</tr>
<tr>
<td>Fever</td>
<td>53.3%</td>
</tr>
<tr>
<td>Mononeuritis multiplex</td>
<td>57.6%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>50.6%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48.2%</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
<td>34.1%</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>30.6%</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>24.7%</td>
</tr>
<tr>
<td>Digital ischaemia</td>
<td>11.8%</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

Percentages reflecting the frequency of involvement in a study group of 85 patients positive for microscopic polyangiitis. Adapted from Guillemin et al.
Clinical Evidence — Call for contributors

Clinical Evidence is a regularly updated evidence-based journal available worldwide both as a paper version and on the internet. Clinical Evidence needs to recruit a number of new contributors. Contributors are healthcare professionals or epidemiologists with experience in evidence-based medicine and the ability to write in a concise and structured way.

Areas for which we are currently seeking authors:
- Child health: nocturnal enuresis
- Eye disorders: bacterial conjunctivitis
- Male health: prostate cancer (metastatic)
- Women's health: pre-menstrual syndrome; pyelonephritis in non-pregnant women

However, we are always looking for others, so do not let this list discourage you.

Being a contributor involves:
- Selecting from a validated, screened search (performed by in-house Information Specialists) epidemiologically sound studies for inclusion.
- Documenting your decisions about which studies to include on an inclusion and exclusion form, which we keep on file.
- Writing the text to a highly structured template (about 1500–3000 words), using evidence from the final studies chosen, within 8–10 weeks of receiving the literature search.
- Working with Clinical Evidence editors to ensure that the final text meets epidemiological and style standards.
- Updating the text every six months using any new, sound evidence that becomes available.
- To expand the topic to include a new question about once every 12–18 months.

If you would like to become a contributor for Clinical Evidence or require more information about what this involves please send your contact details and a copy of your CV, clearly stating the clinical area you are interested in, to Klara Brunnhuber (kbrunnhuber@bmjgroup.com).

Call for peer reviewers

Clinical Evidence also needs to recruit a number of new peer reviewers specifically with an interest in the clinical areas stated above, and also others related to general practice. Peer reviewers are healthcare professionals or epidemiologists with experience in evidence-based medicine. As a peer reviewer you would be asked for your views on the clinical relevance, validity, and accessibility of specific topics within the journal, and their usefulness to the intended audience (international generalists and healthcare professionals, possibly with limited statistical knowledge). Topics are usually 1500–3000 words in length and we would ask you to review between 2–5 topics per year. The peer review process takes place throughout the year, and our turnaround time for each review is ideally 10–14 days.

If you are interested in becoming a peer reviewer for Clinical Evidence, please complete the peer review questionnaire at www.clinicalevidence.com or contact Klara Brunnhuber (kbrunnhuber@bmjgroup.com).
Causes of severe visual impairment and blindness in schools for visually handicapped children in Iran

S A Mirdehghan, M H Dehghan, M Mohammadpour, K Heidari, M Khosravi

Aims: This survey was conducted on children in schools for the blind in Tehran (from 2002 to 2003) to determine the causes of severe visual impairment and blindness and to identify preventable and treatable conditions.

Methods: The study was performed on 362 students at different grades in three schools for the blind. Patient sex, age, family history of blindness or low vision, visual acuity, causes of blindness, and treatable and preventable conditions were studied.

Results: Of the 362 cases, 210 (58%) were boys and 152 (42%) were girls. Mean age was 13.5 (SD 4) years. Severe visual loss was seen in 80.9%. Retinal diseases were the most common cause for low vision (51%); cataract, optic nerve atrophy, corneal and anterior segment diseases, glaucoma, anophthalmia, and globe malformations were other major causes of blindness. Treatable aetiologies and positive family history of blindness were seen in 25.7% and 36% of the patients, respectively. The incidence of preventable diseases, excluding familial disorders, was low.

Conclusion: In addition to the prevention and treatment of some conditions, premarital genetic counselling and family planning control in families with inherited diseases could decrease the number of blind children in the future in Iran.

Materials and Methods
This study was carried out via interview and examination in three blind educational centres in Tehran, Iran, from 2002 to 2003.

All students at Narjes educational centre and half of the students at Mohebhi educational centre (low vision schools) were examined at the eye clinic of the Labbafinejad Medical Centre. The rest of the students, together with students from Khazaei, were examined at their schools. History taking and eye examination including visual acuity (VA), refraction if possible, anterior segment examination by biomicroscope, fundus examination by indirect ophthalmoscope, and IOP measurement were performed. Data were recorded on special forms, and causes leading to blindness were highlighted regarding the possibility of prevention and treatment. Findings were statistically analysed by software programs. Loss of vision in students was defined according to the blind educational classifications of the special education organisation: visual acuity between 20/200 and 20/80 in the better eye, so that the patient could read large optotypes with maximum correction and could educate at ordinary schools, was defined as mild visual loss. Visual acuity between 10/200 and 20/200 in the better eye, so that the patients could walk but not read large optotypes and should learn the Braille system, was defined as moderate loss of vision. Visual acuity between no light perception and 10/200 in the better eye, so that the patient is absolutely blind, was defined as severe visual loss. These patients must learn the Braille system and other skills to increase individual abilities for orientation and learning.

Results
A total of 362 patients with mean age of 13.5 (SD 4) years (range 5–25 years) were included in this survey, 210 (58%) were male and 152 (42%) were female. Family history of blindness was reported in 131 (36%), which included 38.2%...
of the girls and 34.8% of the boys. Figure 1 shows the cause of decreased vision in the studied cases: more than 80% of patients had severe visual loss.

Figure 2 shows the prevalence of causes of blindness. Retinal diseases were the most common cause of blindness, followed by cataract, optic nerve atrophy, and glaucoma. Phthisis bulbi in two, trauma in three, neoplasia in one, and uveal coloboma in six cases had a minimal role in causing blindness (fig 2).

Table 1 indicates the distribution of diseases leading to blindness. Leber’s congenital amaurosis (LCA) was the most common disease, present in 160 cases (44.2%) and is untreatable and unpreventable. The most common preventable disease was secondary atrophy of the optic nerve with a prevalence of 13.5%, followed by congenital glaucoma with a prevalence of 7.5%. Retinal detachment, familial exudative vitreoretinopathy (FEVR), anophthalmia, cortical blindness and phthisis bulbi, congenital retinal detachment, Usher syndrome and corneal endothelial dystrophy, Ehler-Danlos syndrome, and retino-blastoma were other causes of blindness.

One hundred eighty five patients (51%) had retinal diseases; the most common disorder in this group was LCA with 160 patients (86.5%).

There are several causes for severe visual impairment in children and some of them are preventable. Secondary atrophy of the optic nerve, congenital toxoplasmosis, and cataract secondary to intrauterine infection were detected in 15 patients and comprised 4.1% of preventable causes of blindness. If inherited diseases are added to acquired diseases more frequency will be obtained; however, since the determination of inherited diseases needs a study with better facilities, this group of diseases was not included in the preventable diseases group. Therefore, most disorders were categorised as unpreventable. Ninety three patients (25.7%) had treatable disorders, which mostly included cataract, glaucoma, anterior segment diseases, secondary atrophy of the optic nerve and, rarely, retinal diseases.

Retinal diseases were the most common untreatable diseases (68% of cases) (table 2).

### DISCUSSION

The prevalence of childhood blindness was reported as 0.17% in southern India. Blindness was caused by treatable refractive errors (33.3%) followed by preventable causes (16.6% the result of vitamin A deficiency and 8.3% the result of amblyopia after cataract surgery). The major remaining causes of blindness were congenital eye anomalies (16.7%) and retinal degeneration (16.7%). The authors concluded that the priorities for action to reduce childhood blindness in India are refractive error, cataract related amblyopia, and corneal diseases. We did not evaluate overall causes of childhood blindness in our population but only the prevalence of causes of blindness in pupils in schools for the blind. Regarding frequency of retinal diseases, LCA, with 160 patients (86.5%), was the most frequent disease; other retinal diseases were less frequent as indicated in table 2. Seventy seven (48.1%) patients with LCA had a positive family history of blindness.

Kello and Gilbert studied causes of severe visual impairment and blindness in Ethiopia and concluded that vitamin A deficiency and measles were the major causes of severe visual impairment/blindness in children in schools for the blind. Most causes are preventable during childhood through provision of basic primary healthcare services. This shows the role of socioeconomic conditions in epidemiology of blindness in underdeveloped countries.

We did not have any proved case of vitamin A deficiency in our series.

### Table 1: Frequency of causes of blindness in schools for the blind in Tehran in 2002-3

<table>
<thead>
<tr>
<th>Diseases</th>
<th>No of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leber’s congenital amaurosis (LCA)</td>
<td>160</td>
<td>44.2</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>49</td>
<td>13.5</td>
</tr>
<tr>
<td>Congenital glaucoma</td>
<td>27</td>
<td>7.5</td>
</tr>
<tr>
<td>Secondary optic atrophy</td>
<td>21</td>
<td>5.8</td>
</tr>
<tr>
<td>Primary optic atrophy</td>
<td>16</td>
<td>4.4</td>
</tr>
<tr>
<td>Peter’s anomaly</td>
<td>12</td>
<td>3.3</td>
</tr>
<tr>
<td>Anophthalmia</td>
<td>11</td>
<td>3.0</td>
</tr>
<tr>
<td>Anterior segment dysgenesis</td>
<td>8</td>
<td>2.2</td>
</tr>
<tr>
<td>Microcornea</td>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>Uveal coloboma</td>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>Rod monochromatism</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>Congenital toxoplasmosis</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>Bardet-Biedel syndrome</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>Sclerocornea</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>Albinism</td>
<td>4</td>
<td>1.1</td>
</tr>
<tr>
<td>Microphthalmia</td>
<td>4</td>
<td>1.1</td>
</tr>
<tr>
<td>Trauma</td>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>Others</td>
<td>15</td>
<td>4.1</td>
</tr>
<tr>
<td>Total</td>
<td>362</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 2: Frequency of retinal diseases among students in Tehran low vision schools 2002-3

<table>
<thead>
<tr>
<th>Diseases</th>
<th>No of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCA</td>
<td>160</td>
<td>86.5</td>
</tr>
<tr>
<td>Rod monochromatism</td>
<td>5</td>
<td>2.7</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Albinism</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>Congenital toxoplasmosis</td>
<td>5</td>
<td>2.7</td>
</tr>
<tr>
<td>FEVR</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Congenital retinal detachment</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Bardet-Biedel syndrome</td>
<td>5</td>
<td>2.7</td>
</tr>
<tr>
<td>Usher syndrome</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Total</td>
<td>185</td>
<td>100</td>
</tr>
</tbody>
</table>
About 36.2% of the students had a positive history of blindness in their families and relatives. No significant difference was seen in family history of blindness in both sexes. To our knowledge, this variable has not been studied in other reports to date.

Severe visual loss was the most frequent type. There was no significant difference in loss of vision between boys and girls; in other words, boys and girls were distributed equally in the three groups of visual loss (mild, moderate, and severe).

Retinal disorders, with a frequency of 51.1%, were the most common cause of blindness: LCA is transferred in an autosomal recessive pattern. Amini reported that the most common diseases leading to blindness were retinal dystrophy followed by optic nerve atrophy and cataract.

In 1988, Schwab performed a study in two schools for the blind in Zimbabwe, which indicated that the cause of blindness in 75% of students was bilateral corneal opacity. In a study carried out in 1992 by Antonowicz, 100 patients aged 3–18 years were studied in a blind centre in a Polish city. The causes of blindness or low vision in order of frequency were as follows: refractive errors, optic nerve atrophy, congenital cataract, retinal and choroidal degeneration, neoplasia, anophthalmia or globe malformations, iris or choroidal coloboma, retinoblastoma, ocular trauma, and congenital glaucoma.

In 1992 a study was performed at six schools for the blind in Ethiopia by Gebriel. Causes of blindness were corneal opacity or phthisis bulbi in 70% and cataract in 14%. In another survey conducted in southern Australia by Newland, data from 3520 patients under 6 years of age were collected and the cause of blindness was cataract in 85% of cases. A study carried out by Cook indicated that senile cataract and chronic glaucoma were the main causes of blindness.

Because of the low incidence of some diseases in some subgroups, it was not possible to determine the significance of the difference in both sexes; however, the sexual dominancy could be determined in any disease. Preventable causes of blindness were as follows: secondary atrophy of the optic nerve, cortical blindness due to trauma, congenital toxoplasmosis, retinal detachment, and cataract secondary to intrauterine infections.

Forty per cent of preventable causes were seen in males and 60% in females; thus the frequency of preventable causes was different in the two sexes. The frequency of treatable diseases was 25.7%, based on primary aetiology of blindness. Retinal diseases, with 185 patients (68%), are the most common untreatable cause of blindness. Cataract, glaucoma, corneal and anterior segment diseases, secondary atrophy of the optic nerve, and rare retinal diseases were among the treatable diseases. In Gilbert’s study, treatable and preventable disorders in Chile, South Africa, and India were 54%, 70%, and 48%, respectively. The prevalence of treatable and preventable diseases in students from Tehran blind schools was 30.1%, which is lower than in Gilbert’s study. Because retinal diseases are the most common untreatable diseases, particularly LCA, it seems that despite measures taken to treat and prevent such disorders, a considerable number of children had (about 70%) developed untreatable and preventable diseases.

In conclusion, severe loss of vision was the most common type of visual loss in schools for the blind in Tehran. Retinal diseases, mostly Leber’s congenital amaurosis, are the most common disorders leading to blindness. These diseases mostly have an autosomal recessive pattern and parents transmit the recessive gene to their offspring usually by consanguineous marriages. Other diseases such as congenital cataract, optic nerve atrophy, anterior segment and corneal diseases, and glaucoma had lower frequencies.

ACKNOWLEDGMENTS
The authors thank colleagues at the eye clinic, Labbafinejad Medical Center, Tehran blind educational centres, Miss Kasmaie, Mr Abdi, and the authorities of Narijs, Shaheed Muhbibbi, and Shaheed Khaza’eli educational institutions.

Authors’ affiliations
S A Mirdehghan, M H Dehghan, M Mohammadpour, K Heidari, M Khosravi, 9th Boosant, Pasdaran Street, Labbafinejad Medical Center, Ophthalmic Research Center, Tehran, Iran

The authors have received no financial support.

REFERENCES
How patients experience progressive loss of visual function: a model of adjustment using qualitative methods

R Z Hayeems, G Geller, D Finkelstein, R R Faden

Background: People with retinitis pigmentosa (RP) experience functional and psychological challenges as they adjust to progressive loss of visual function. The authors aimed to understand better the process of adjusting to RP in light of the emotional suffering associated with this process.

Methods: Adults with RP were recruited from the Foundation Fighting Blindness and the Wilmer Eye Institute in Baltimore. Focus groups and semistructured interviews addressed the process of adjusting to RP and were audiorecorded and transcribed. The transcripts were analysed qualitatively in order to generate a model of adjustment.

Results: A total of 43 individuals participated. It was found that, on diagnosis, people with RP seek to understand its meaning in their lives. Mastering the progressive functional implications associated with RP is contingent upon shifting personal identity from a sighted to a visually impaired person. In this sample, six participants self-identified as sighted; 10 self-identified as in transition, and 27 self-identified as visually impaired. This adjustment process can be understood in terms of a five-stage model of behaviour change.

Conclusions: The proposed model presents one way to understand the process of adjusting to RP and could assist ophthalmologists in meeting their moral obligation to lessen patients’ suffering, which arises in the course of their adjustment to progressive loss of visual function.

R etinitis pigmentosa (RP) is a relatively common type of progressive diffuse retinal degeneration. There is no prevention, cure, or means to restore retinal function. Adjusting to RP inevitably entails a certain degree of suffering. Suffering can be defined as a state of distress that occurs when a person’s integrity or life plan is threatened, disrupted, or burdened; it lasts until integrity is restored, either by eliminating the threat or adjusting to it. It is not the physical impairments themselves, but the impact of the physical state on the person as a whole that causes suffering. This has been referred to as “existential suffering.” It is arguably the case that physicians are morally obligated to lessen suffering in their patients. In the case of RP, where there is little that physicians can do to alter the course of retinal degeneration, one means by which to lessen suffering is to participate in patients’ process of adjusting to it.

When people with RP confront challenges related to education, employment, mobility, and socialisation, use of assistive technology, and mental health, suffering may manifest as denial, anger, fear, or depression. Despite what is known about these challenges, the process of adjusting to vision loss is only touched upon in the clinical ophthalmology literature. It has been reported that the presence of role models, social supports, and a positive doctor-patient relationship may influence adjustment. By developing an appreciation of their patients’ adjustment process, ophthalmologists would be doing more than fostering a positive doctor-patient relationship. They would, it has been argued, be meeting a moral obligation to understand the lived experiences of their patients as a means by which to lessen patient suffering.

In light of the limitations in the quantitative literature to date, we set out to explore the process of adjusting to the loss of visual function associated with RP through a qualitative approach. In this paper we report our findings and develop a model for ophthalmologists to consider in their effort to understand and lessen their patients’ suffering. Seven practical steps are suggested as means by which to incorporate this model into clinical practice.

METHODS

While quantitative tools are available to “measure” the extent to which someone has adjusted to a given circumstance, a qualitative approach better captures the essence of the adjustment process and factors that influence its course that may not be revealed by available quantitative tools. For this reason, we chose to use qualitative methodology.

Adults with RP were recruited from the Baltimore chapter of the Foundation Fighting Blindness (FFB) and The Wilmer Eye Institute at Johns Hopkins Hospital. FFB registrants were stratified into three predetermined age categories before recruitment since these data were available at this time, whereas Wilmer patients were stratified according to age following a preliminary screening questionnaire to determine eligibility (table 1). This theoretical sampling technique enabled us to collect data that reflected the adjustment process at various life stages. By telephone or mail, all eligible individuals were invited to participate. Consent was obtained by a paper or by voice recorded consent. This study was approved by the joint committee of clinical investigation at Johns Hopkins Medical Institute.

Data were collected through semistructured interviews and focus groups. Three focus groups were conducted by trained moderators, lasted 2 hours, and were transcribed by court stenographers. Telephone interviews were conducted by trained interviewers, were approximately 45 minutes in duration, and were audiorecorded and transcribed.

Transcripts were analysed qualitatively (see appendix). The end product of our analysis is a process oriented model that depicts the relationships among the codes and the core category. Demographic data were analysed descriptively.

Abbreviations: FFB, Foundation Fighting Blindness; RP, retinitis pigmentosa
Sample
In all, 43/88 individuals agreed to participate (response rate 49%). Table 2 presents demographic data on participants. Among non-participants for whom demographic data were available (32/45; FFB registrants only), the mean age at the time of recruitment was 51 years and mean age of diagnosis was 26 years; 67% were male and 25% had a known family history of RP.

RESULTS
The qualitative data presented below illustrate particularly salient themes reflected by the majority of participants. Each theme is placed in the context of the adjustment model, illustrated diagrammatically in figure 1. Participants’ sex, age at participation, and age at diagnosis are indicated following their remarks.

Diagnostic experience and reactions
Participants described a range of reactions at the time of their diagnosis that were influenced by the way in which physicians communicated the diagnosis to them. When physicians used what the majority of participants described as “blunt” language, participants described feeling devastated:

- “He said, ‘by the time you’re 50 you’re not going to be able to drive. You’re not going to be able to read by the time...”

Table 1 Recruitment stratification (theoretical sampling frame)

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>0–18 years</td>
<td>18–35 years</td>
</tr>
<tr>
<td>Age at study participation</td>
<td>0–35 years</td>
<td>35–50 years</td>
</tr>
</tbody>
</table>

Table 2 Demographic characteristics of participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age group 1</th>
<th>Age group 2</th>
<th>Age group 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(x/8)</td>
<td>(x/19)</td>
<td>(x/16)</td>
<td>(x/43)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (62%)</td>
<td>11 (58%)</td>
<td>8 (50%)</td>
<td>24 (56%)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (38%)</td>
<td>8 (42%)</td>
<td>8 (50%)</td>
<td>19 (44%)</td>
</tr>
<tr>
<td>Age now</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>33.5 (21.44)</td>
<td>49 (39.77)</td>
<td>61 (49.79)</td>
<td>48 (21.79)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>15 (4.5)</td>
<td>18 (5.3)</td>
<td>41 (27.52)</td>
<td>25 (4.5)2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8 (100%)</td>
<td>16 (84%)</td>
<td>16 (100%)</td>
<td>40 (93%)</td>
</tr>
<tr>
<td>African-American</td>
<td>0</td>
<td>3 (16%)</td>
<td>0</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catholic</td>
<td>3 (38%)</td>
<td>5 (26%)</td>
<td>5 (31%)</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Protestant</td>
<td>4 (50%)</td>
<td>9 (47%)</td>
<td>7 (44%)</td>
<td>20 (46%)</td>
</tr>
<tr>
<td>Jewish</td>
<td>1 (12%)</td>
<td>0 (0%)</td>
<td>4 (25%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Other/none</td>
<td>0 (0%)</td>
<td>5 (26%)</td>
<td>0 (0%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Relationship status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>6 (75%)</td>
<td>13 (68%)</td>
<td>14 (88%)</td>
<td>33 (77%)</td>
</tr>
<tr>
<td>Single</td>
<td>2 (25%)</td>
<td>3 (16%)</td>
<td>0 (0%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Partner</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
<td>0 (0%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Widowed</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>1 (6%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Grade level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>0 (0%)</td>
<td>3 (16%)</td>
<td>5 (31%)</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>Some college</td>
<td>3 (38%)</td>
<td>9 (47%)</td>
<td>3 (19%)</td>
<td>15 (35%)</td>
</tr>
<tr>
<td>4 years at college</td>
<td>3 (38%)</td>
<td>4 (21%)</td>
<td>3 (19%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>Post grad school</td>
<td>2 (25%)</td>
<td>3 (16%)</td>
<td>5 (31%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$20 000</td>
<td>0 (0%)</td>
<td>4 (21%)</td>
<td>1 (0.6%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>$20 000–$34 999</td>
<td>1 (12%)</td>
<td>3 (16%)</td>
<td>5 (31%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>$35 000–$49 999</td>
<td>1 (12%)</td>
<td>4 (21%)</td>
<td>1 (0.6%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>$50 000–$74 999</td>
<td>1 (12%)</td>
<td>5 (26%)</td>
<td>3 (2%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>&gt;$75 000</td>
<td>5 (62%)</td>
<td>3 (16%)</td>
<td>6 (38%)</td>
<td>14 (32%)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full time</td>
<td>5 (62%)</td>
<td>8 (42%)</td>
<td>4 (25%)</td>
<td>17 (40%)</td>
</tr>
<tr>
<td>Part time</td>
<td>1 (12%)</td>
<td>2 (11%)</td>
<td>3 (19%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Retired</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>7 (44%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>2 (25%)</td>
<td>9 (47%)</td>
<td>2 (12%)</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Affiliation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFB</td>
<td>7 (88%)</td>
<td>15 (79%)</td>
<td>13 (81%)</td>
<td>35 (81%)</td>
</tr>
<tr>
<td>Support group</td>
<td>3 (38%)</td>
<td>8 (42%)</td>
<td>9 (56%)</td>
<td>20 (46%)</td>
</tr>
<tr>
<td>Family history of RP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>3 (38%)</td>
<td>3 (16%)</td>
<td>1 (6%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Absent</td>
<td>4 (50%)</td>
<td>10 (53%)</td>
<td>13 (81%)</td>
<td>27 (63%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (12%)</td>
<td>6 (32%)</td>
<td>2 (12%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>Self identified as</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sighted</td>
<td>2 (25%)</td>
<td>2 (10%)</td>
<td>2 (12%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>In transition</td>
<td>3 (38%)</td>
<td>2 (10%)</td>
<td>5 (31%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>Visually impaired</td>
<td>3 (38%)</td>
<td>15 (80%)</td>
<td>9 (56%)</td>
<td>27 (63%)</td>
</tr>
</tbody>
</table>
you’re 60 or see light by the time you’re 70.’ I was completely devastated. I was 30 years old… the end of my life felt like it occurred that day.” (F55/30)

When physicians used what some participants described as “vague” language, participants described feeling anxious:
- “He told me I had RP but didn’t tell me I would likely go blind. I didn’t know what it was…I went through a lot of anxiety attacks because I had no knowledge of what was actually going to happen…” (M62/40)

In contrast, when physicians used what some participants described as “mild” language, many participants felt hopeful:
- “He said, ‘it’s a progressive disease. It’s a long slow process…you’re not going to have any immediate problems, it could happen in five years or in 50 years’…so I chose to hope it would happen in 50 and move on…” (M56/15)

Meaning
In order to make sense of their diagnosis, all participants searched to understand why it happened. Many participants considered both genetic and non-genetic causes of RP:
- “either I got it from a hard blow to the head or I inherited it…since nobody going back has it they narrowed it down to when I fell down the stairs.” (F35/22)

And some participants used spirituality to reflect on this question:
- “You wonder, God, why is it me? Well, maybe I’m an inspiration to someone, maybe I’m affecting other people’s lives positively…maybe that’s the reason.” (M42/27)

Personal identity
For most participants, resolving personal identity as a sighted versus a visually impaired person posed an early and pivotal challenge. We deemed personal identity to be the core variable of our analysis since participants’ described their adjustment as contingent upon it:
- “Now I’m just sort of lost in between…one of the hardest things for me has been not feeling like a sighted person and not feeling like a blind person. I’ve gotten to know some blind people and seen how amazingly well they’ve adapted and then I see my sighted friends, and then I see myself, and I am neither. I feel like I am going to be inferior until I am either or.” (M21/6)
- “What was particularly vexing for me, since it is so slow, you really have a hard time putting your finger on when it is you need to change the way you do this or that, how you present yourself to other people…” (M62/37)

Course of action
Two courses of action emerged as participants were in the process of resolving their personal identity.

Figure 1, course A (self identified as sighted)
At various ages, six participants identified as sighted and resisted using assistive devices and making lifestyle changes (table 2). They described making an effort to conceal any evidence of visual impairment.
- “I’m not at the point where I’m comfortable with the idea of people looking at me differently. If I wear my contacts I look totally normal and people just don’t know.” (F29/16)
- “I do my own private little shopping…I hate the stores…I order whatever over the phone, flip out my credit card, and UPS delivers it to my door.” (F54/20)

Figure 1, Course B (self identified as visually impaired)
Irrespective of their age, 27 participants identified as visually impaired and described assistive devices and certain lifestyle changes as adaptive (table 2) because they:
1. explain RP to others: “…the stick lets everybody know that when I walk into a pole or bump into them, there is a reason for it.” (M57/21)
2. promote independence: “To me the cane is gonna let me walk without tripping, and get places that I wouldn’t be able to go.” (M24/18)
3. promote competence: “I worked nights and weekends to learn these computer programs because my goal was to be more proficient than anybody…and then my boss put me in charge of computerising the entire department.” (M42/27)
4. promote safety: “[my guide dog] takes me downtown to work…I feel more at ease because I know she won’t let anything like a car come at me…” (M62/40)

Behaviour change
Course A appears to act as a default path until individuals make certain behavioural and/or lifestyle changes and approach course B. Our data illustrate various stages between course A and course B. Ten participants, between the ages of 21 and 59 identified themselves as in transition between sighted and visually impaired (table 2). They could acknowledge some of the benefits of assistive devices but were not ready to use them:
• “I would like that visible symbol for people to know and understand...but I wish there was something other than a cane.” (F49/38)

Five of these ten participants expressed tentative readiness to make changes:

• “I look totally normal with my glasses on, but then I put those clips on, like my parents do...I’m not even 30...I’m forcing myself to wear them around my comfort zone but I haven’t gone out with them yet.” (F29/16)

Three participants who were currently further along in their transition process described their adaptive steps. For example,

• “(the mobility trainer) said...before you go out the door, you pick up your purse and you pick up your cane ...then my husband came home and said let's go out for dinner, grab your cane...okay, here we go, so I get outside and I open my cane...” (F50/18)

Others reflected on new ways of meeting their same goals:

• “I’m not able to play basketball or golf anymore...so I’ve tried independent sports where I can still challenge and exercise myself like roller-blading and wind-surfing.” (M34/6)

Some participants recalled vacillating between ambiguous identities and related behaviours. For example,

• “There was a time when I used to drive a car and use a cane. I would keep the cane concealed underneath the dash and use the cane at night.” (F55/30)

As well, many participants reflected on the continuous processing required as they encountered new functional limitations over time, irrespective of age:

• “At any age...you’re constantly in flux. You get to levels of acceptance and levels of accomplishment and then it gets a little worse so you drop down a step and then you need another apparatus...every step is a process to where you’re going...you have to be mentally strong and self confident because you get knocked down and have tough days...but you have to keep moving forward.” (M42/27)

Ultimately, once participants viewed behavioural and lifestyle changes as personal benefit rather than as social risk, adaptive changes became integrated into their lives:

• “I discovered that [the cane] was positively liberating. It means I don’t have to have someone with me and I can go out anytime anywhere by myself.” (M62/37)

Many participants referred to their public use of assistive devices as “outing” themselves:

• “Once you’re ‘out,’ the cane is the only way you know.” (M49/16)

Self esteem
All participants described self esteem as critical to moving through this continuum. This was particularly salient among younger participants and participants in transition:

• “Sure I’ve had my inferiority problems...I’ve been ashamed that I couldn’t be the one to drive and macho stuff like that...that was a low point for me.” (M24/18)

• “I try to feel good about myself in other ways. I keep myself in shape, do my hair and make-up, so if people look at me and see me with dark glasses and a cane, I can still look and feel attractive...” (F29/16)

DISCUSSION
Ages of participants and non-participants at the time of participation and diagnosis were similar (48 years and 51 years, respectively, 25 years and 26 years respectively). While there were more male than female non-participants, there were also more male participants. The X linked pattern of inheritance that can be associated with RP may account for a greater proportion of males in this population in general. Participation did not appear to be a function of age or sex therefore these variables are unlikely to have affected the nature of the model developed. Family history was slightly more common among non-participants. Perhaps those with a family history perceived adjustment as a family norm rather than as a process that required significant exploration. We could speculate, therefore, that the model presented better applies to individuals who do not have a known family history of RP.

Adjustment model
Our data suggest that the process of adjusting to RP is a dynamic one composed of a series of inter-related steps. As stated in the appendix, we found our data to be consistent with certain existing concepts in the adjustment literature. The search for meaning involves understanding why a disability has occurred. Mastery centres around gaining control over the implications in order to manage them. Self esteem reflects the effort to regain a positive view of oneself in a new life situation.

Applying in-depth qualitative analysis techniques to participants’ personal stories, we were able to construct a model that reflects true lived experiences rather than objective measurements that emerge from highly structured quantitative approaches. We found that adjustment proceeds as follows (fig 1). The diagnostic experience combined with individuals’ reactions to it can lead to emotional suffering. In response, individuals search to understand the meaning and cause of their RP; they attribute causation to inheritance, childhood accidents, and spiritual intervention. Functional limitations ensue and challenge a person’s integrity. Mastering these limitations is motivated, in part, by that person’s interest in reducing his/her own suffering and appears to be contingent upon resolving personal identity as a sighted or visually impaired person. This may involve changing deeply engrained behaviours, a process that has been described as a series of five stages. The stage of precontemplation characterised those who did not need to change behaviour, had not acknowledged their need to change, or were not ready to change. During contemplation, participants reflected the profound ambivalence between sighted and visually impaired identities. In this phase, the disadvantages of changing outweighed the advantages. As the balance began to tip, participants reflected plans to give up driving or to take mobility training as examples of the preparation stage and continued to move through the action phase as they began to use assistive devices in public or find novel solutions to their limitations. The action stage was characterised by participants “outing” themselves. Once they were “out,” the benefits of independence and competence outweighed previously perceived social risks. This shift enabled these adjustments to be maintained. Ultimately, adjustment was achieved when individuals self identified as visually impaired, revealed their RP, used assistive devices, and made lifestyle changes in order to regain self esteem and independence. Since the behavioural, lifestyle, and psychological changes that constitute
adjustment appear to be contingent upon participants’ identity as sighted or visually impaired, personal identity was deemed the core category of this model.

It is noteworthy that responses among participants in various age categories were relatively consistent. Our sample reflected preliminary (sighted identity described by six participants), transitional (ambiguous identity described by 10 participants), and final (visually impaired described by 27 participants) stages of this process. Since each age group was represented in each of these identity categories, we suggest that, although the task at hand may vary with age or stage of life, the core assumptions of the model can be used to navigate adjustment at any age.

Using quantitative methodology, Dods et al. developed an adjustment model that specified internal self worth and self as agent as key variables and suggested that these variables be integrated into a cognitively oriented therapeutic approach with patients. Zaborowski endorsed this approach by suggesting that adjusting to blindness requires an individual to make a cognitive shift which acknowledges that being blind can be compatible with remaining functionally independent. This suggests that a healthcare provider could use our model as a tool by which to help their patients approach this necessary cognitive shift in personal identity.

Limitations
This model reflects only one interpretation of these data. Specific limitations are highlighted in table 3.

Contribution to the literature
Our data support an integration of adjustment and behaviour change theories by illustrating how adjustment implicates behaviour change through the construct of personal identity. Our data add to the suffering literature by providing a concrete clinical example of the distinction between “symptom related” suffering and “existential” suffering.

Finally, we believe that this model may be of particular importance since it is patient driven and, hopefully, of clinical value to physicians. As physicians endeavour to lessen suffering, addressing personal identity with patients is paramount. Physicians can better fulfill their moral obligation to lessen suffering by contributing to identity resolution and adjustment. Practical steps by which to do so are outlined in table 4. Rather than reacting to suffering after it presents, this model may help ophthalmologists be proactive in helping their patients resolve personal identity conflicts. Ophthalmologists can fine tune their care in order to lessen patients’ suffering that arises in the course of their adjustment to progressive loss of vision.

ACKNOWLEDGEMENTS
We thank Stephanie Rice Davis, MSW, for contributing to the original project proposal and facilitating communication with the donors.
We thank Julia Slutsman, PhD, for assisting with the qualitative analysis of these data.
This project was made possible by an anonymous gift.

Table 4 Seven practical steps for ophthalmologists to integrate into practice

<table>
<thead>
<tr>
<th>Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Understand the meaning patients ascribe to their diagnosis</td>
</tr>
<tr>
<td>(2) Recognise and acknowledge the manifestations of an unresolved</td>
</tr>
<tr>
<td>identity (concealing RP, avoiding adaptive change)</td>
</tr>
<tr>
<td>(3) Normalize any personal identity conflict patients express by</td>
</tr>
<tr>
<td>(anonymously) sharing similar conflicts experienced by other patients, for example</td>
</tr>
<tr>
<td>(4) Help patients weigh the advantages and disadvantages of behaviour</td>
</tr>
<tr>
<td>and lifestyle changes</td>
</tr>
<tr>
<td>(5) Tailor their dialogue and recommendations to patients’ functional</td>
</tr>
<tr>
<td>and psychological readiness for change</td>
</tr>
<tr>
<td>(6) Acknowledge patients’ progress</td>
</tr>
<tr>
<td>(7) Provide guidance and supportive resources in anticipation of this</td>
</tr>
<tr>
<td>suffering in order to facilitate smooth and adaptive transitions</td>
</tr>
</tbody>
</table>

APPENDIX

QUALITATIVE ANALYSIS
Criteria used to identify salient themes within the transcripts included: (1) text that described key elements of the participants’ adjustment processes and (a) recurred in multiple transcripts, (b) recurred in both telephone interview and focus group transcripts, or (c) recurred among participants in different demographic categories (for example, age, sex groups). Salient themes were then assigned codes. Some codes reflected direct responses to interview questions and other codes emerged from the experiences shared by participants over the course of the interview or discussion. The theme upon which adjustment was deemed to be contingent by the majority of participants was considered to be the core category.

A qualitative analysis software package called Nvivo was used to organise the coded data. Nvivo enables the analyst to code text as it is reviewed, quantify the frequency of relevant themes across transcripts, and discern relations among salient themes by way of coding trees and conceptual maps.

While telephone interview and focus group data reflected different experiences and emphases on some topics, themes pertinent to the adjustment process and captured by the proposed model were similar. For this reason, these data were combined for the purpose of this paper.

We integrated the concepts generated from our data with related concepts reported in the literature. Specifically, meaning, mastery, self esteem, and the five stages of behaviour change are constructs derived from the literature.
that support the data generated. The components of the adaptive courses (course A and course B), the construct of personal identity, and the relation among all of these components of the model emerged from the data themselves.

REFERENCES

35 NVivo—Nud*ist for qualitative research. Australia: Qualitative Solutions and Research Pty Ltd 1999.
The development of the Indian vision function questionnaire: field testing and psychometric evaluation

S K Gupta, K Viswanath, R D Thulasiraj, G V S Murthy, D L Lamping, S C Smith, M Donoghue, A E Fletcher

Objective: To develop and evaluate the acceptability, reliability, validity, and responsiveness of the Indian vision function questionnaire (IND-VFQ).

Methods: Problem statements from previous qualitative studies were reduced to a 45 item interviewer administered questionnaire representing three a priori domains (general functioning, psychosocial impact, and visual symptoms) which was evaluated in patients with cataract (n = 420), glaucoma (n = 120), diabetic retinopathy, or age related macular degeneration (n = 120) and normal controls (n = 120). Standard methods were used for item reduction and to evaluate psychometric properties.

Results: Psychometric item reduction produced a 33 item questionnaire. Psychometric evaluation showed that two of the three scales (psychosocial impact and visual symptoms) had good acceptability, and that all three scales showed high internal consistency (alpha > 0.80; item-total correlations 0.54–0.86) and test-retest reliability (>0.89). All three scales showed moderate evidence of convergent and discriminant validity. Responsiveness, assessed in cataract patients (n = 120) before and after surgery, was good for all three scales (effect sizes >1).

Conclusions: The IND-VFQ33 is a psychometrically sound measure of vision function addressing a gap in patient defined measures of vision function developed in populations living in low income countries.

METHODS AND PARTICIPANTS

Instrument development

In a previous paper we described how patients participated in the content development of the IND-VFQ by identifying the impact their vision problems had on their daily lives and psychosocial wellbeing. Approximately 5000 elicited problem statements grouped into 18 domain areas were reduced to 210 statements through a process of merging statements with a similar semantic meaning and context. We undertook a further process of item reduction by eliminating statements with low frequency counts (defined as problems reported by less than 10% of the patient population). This process resulted in 103 statements for inclusion in a draft questionnaire for preliminary field testing.

Visual symptoms, psychosocial impact, and general functioning questions were assessed by a four point response scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = a lot) that was identical to that used in the Madurai Intra-Ocular Lens Study quality of life instrument. An extra response category (which scored 5) was included in the general functioning domain to reflect the respondent’s inability to carry out the activity because of vision impairment. The final field test version of the questionnaire also included one open ended question that asked patients if there were any other ways that their eye problem affected their lives. This query did not yield any new information that was not already covered in the questionnaire.

After preliminary field testing for face validity and acceptability, the 103 item IND-VFQ was administered to a total of 96 patients equally divided across the three study centres: Dr Rajendra Prasad Centre for Ophthalmic Sciences, Delhi (RPC), Sarojini Devi Eye Hospital, Hyderabad, and Aravind Eye Hospital, Madurai. Sixty cataract patients (30 recruited via community based clinics linked to each study hospital and 30 hospital inpatients); 18 hospital outpatient glaucoma patients; and 18 hospital outpatients with diabetic retinopathy or age related macular degeneration (case definitions are described elsewhere). Additionally, 30 people without ocular pathology (defined as visual acuity ≥ 6/12 in the presenting better eye) who constituted a normal comparison group, were also administered the draft questionnaire. Participants in the “normals” comparison group were recruited from the patient “escort” population and were comparable with the patient groups on age, sex, and other relevant sociodemographic variables.

We examined endorsement frequencies for the 103 item questionnaire for the group as a whole (excluding people in the normal comparison group) and separately for the three conditions. Questions were eliminated from the draft questionnaire on the basis of the following criteria:

- More than 10% of respondents endorsed the response category “Don’t do this for other reasons.” A total of 18 questions were eliminated on the basis of this criterion.

Abbreviations: IND-VFQ, Indian vision function questionnaire
More than 30% of respondents selected the response “Not at all.” A total of 40 questions were eliminated on the basis of this criterion.

This process resulted in a 45 item questionnaire with three scales: general functioning (28 questions), psychosocial impact (nine questions), and visual symptoms (eight questions). These three scales were adopted because they captured the semantic flavour of patient identified problems of function, behaviour, feelings, and symptoms rather than a clinically derived taxonomy of problems. Each scale was scored using a simple addition of the values according to the response scales. For example, general functioning scores could range from 28 (no problems on all items in this domain) to 140 (maximum responses on all items). Before questionnaire administration, all language versions of the questionnaire satisfied independent translation and back translation from English into local mother tongue languages of Hindi, Telegu, and Tamil.

Field testing the 45 item IND-VFQ

Study population

We aimed to recruit 780 participants, including 660 patients who satisfied predefined clinical criteria (described elsewhere1) for cataract, glaucoma, and retinal conditions (diabetic retinopathy and macular degeneration) in equal numbers from the three study centres, all leading ophthalmic hospitals, located in New Delhi, Hyderabad, and Madurai, and 120 normal controls. The target number of participants were cataract (n = 420), of which 120 were to be recruited through hospital outpatient departments before surgery and 300 through community outreach camps before surgery;

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Psychometric tests and criteria (adapted from Lamping et al)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychometric property</td>
<td>Definition</td>
</tr>
<tr>
<td>1 Item reduction</td>
<td>Identify items for possible elimination</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Acceptability</td>
<td>Completeness of data and score distributions</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Reliability</td>
<td>The extent to which items comprising a scale measure the same construct</td>
</tr>
<tr>
<td>3.1 Internal consistency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2 Test-retest reliability</td>
<td>The stability of an instrument assessed by administering the instrument to respondents on two separate occasions</td>
</tr>
<tr>
<td>4 Validity</td>
<td></td>
</tr>
<tr>
<td>4.1 Content validity</td>
<td>Extent to which content of instrument or scale is representative of intended conceptual domain</td>
</tr>
<tr>
<td>4.2 Construct validity</td>
<td>Evidence that a single construct is being measured</td>
</tr>
<tr>
<td>4.2.1 Within scale analyses</td>
<td></td>
</tr>
<tr>
<td>4.2.2 Analyses against external criteria</td>
<td>Evidence that the instrument differentiates between groups who are known to differ—eg, by presence or severity of disease</td>
</tr>
<tr>
<td>4.2.2.1 Known group differences</td>
<td>Expected correlation with visual acuity</td>
</tr>
<tr>
<td>4.2.2.2 Convergent validity</td>
<td>Evidence that the instrument correlates with measures of the same of a similar construct</td>
</tr>
<tr>
<td>4.2.2.3 Discriminant validity</td>
<td>Ability of a scale to detect clinically significant change following a treatment of known efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
glaucosa (n = 120), recruited through hospital outpatient departments; retinal conditions (n = 120), recruited through hospital outpatient departments; and normal controls (n = 120). All cataract patients underwent extracapsular cataract extraction surgery plus intraocular lens implant. Patients who participated in the content development phase and cataract patients scheduled for intracapsular rather than extracapsular extraction were excluded. To evaluate the test/retest reliability of the IND-VFQ, 360 patients (120 hospital recruited cataract patients, 120 glaucoma patients, and 120 patients with retinal conditions) were scheduled for a repeat administration of the questionnaire 1–2 days after the baseline assessment. Responsiveness was evaluated only in cataract patients by administering a second questionnaire 5–8 weeks after intraocular lens surgery. Informed verbal consent was obtained for all study participants. Ethical approval was obtained from respective governing authorities at each study centre.

Questionnaire administration
Interviewers from each study centre attended a training workshop conducted by experienced interviewers from the Tamil Nadu centre. Interviewers were familiarised with the principles of questionnaire administration and supervised in the conduct of practice interviews. During data collection, principal investigators at each centre observed random interviews to ensure their correct conduct, and quality control in questionnaire completion. For glaucoma and retinal patients, baseline interviews were completed before patients had their ophthalmic consultation. Cataract patients completed baseline questionnaires after diagnosis of their eye condition but before surgery. Where possible, the same interviewer who conducted the baseline interview administered the retest and post-surgery questionnaire. All questionnaires were sent to the central coordinating office (Dr Rajendra Prasad Centre) for data entry. SPSS version 11.01 was used for data analyses.

Psychometric evaluation
Standard psychometric methods and criteria were used for item reduction and to evaluate acceptability, reliability, validity, and responsiveness (table 1). All psychometric analyses were performed on the pooled dataset from all three centres. This approach to performing analyses on pooling data across language versions has been used in previous psychometric validations of other commonly used international outcome measures. Item reduction analyses were performed on pooled data for the three patient groups but excluded normal controls. Psychometric analyses were carried out by SS and SG with expert advice from DL.

RESULTS
At baseline, the 45 item IND-VFQ was administered to all 660 patients and 120 controls by the trained interviewers at each study centre (100% response rate). Study participants tended to be elderly with chronic vision impairment, including blindness, often educated to primary/secondary school level yet inclusive of a sizeable illiterate population which is representative of the general population, and mixed in terms of caste composition (table 2). Repeat questionnaires were obtained for 97% (n = 350) of hospital recruited patients (120 cataract, 114 glaucoma, and 116 retinal). Post-surgery questionnaires were obtained for 87% of cataract patients (111 hospital recruited and 255 community recruited). The main reason for non-completion of the questionnaire was failure of the patient to attend.

Item reduction
Item analyses were performed to evaluate the IND-VFQ45 for missing data, redundancy and item convergent/discriminant validity. Four items (all from the general functioning scale) were eliminated because they had >5% missing data. A further eight items were eliminated, six because of inter-item correlations of >0.80 (three from general functioning and three from psychosocial impact) and two for failing tests of item convergent/discriminant validity (one from psychosocial impact and one from visual symptoms). Item reduction analyses thus produced a 33 item questionnaire (IND-VFQ33). All subsequent psychometric tests were performed on the IND-VFQ33 scales: general functioning (Q1–Q21), psychosocial impact (Q22–Q26), and visual symptoms (Q27–Q33).

Psychometric evaluation of the IND-VFQ33
Scores showed the full range from minimum to maximum. The proportion of missing data on each scale was acceptable for psychosocial impact and visual symptoms scales (3.3% and 1.4% respectively) but higher for general functioning (14.5%). The main reason for missing data in the general functioning scale was the respondent did not consider the question relevant. Floor/ceiling effects were low (1% or less) for general functioning and visual symptoms but 6.9% for psychosocial impact. Similarly, ceiling effects tended to be higher for the psychosocial scale (15.7%) compared to general

| Table 2 Sociodemographic characteristics of participants |
|----------------|----------------|----------------|----------------|----------------|
|               | Cataract (n = 420) | Glaucoma (n = 120) | DR/AMD* (n = 120) | Normal (n = 120) |
| Age < 60      | 62%              | 58%             | 45%             | 44%             |
| Female        | 52%              | 48%             | 50%             | 50%             |
| Education:    |                  |                 |                 |                 |
| Illiterate    | 66%              | 62%             | 66%             | 66%             |
| Primary/secondary | 33%           | 62%             | 62%             | 62%             |
| College       | 1%               | 25%             | 21%             | 25%             |
| Caste‡:       |                  |                 |                 |                 |
| Forward caste | 28%              | 55%             | 46%             | 41%             |
| Backward caste| 47%              | 37%             | 40%             | 47%             |
| Scheduled caste| 21%             | 7%              | 8%              | 10%             |
| Visual acuity: better eye |     |                 |                 |                 |
| <6/60–5/60    | 21%              | 3%              | 15%             | Not applicable |
| <3/60         | 2%               | 7%              | 19%             |                 |
| Duration of eye problem |     |                 |                 |                 |
| 3 months–1 year | 70%             | 37%             | 61%             | Not applicable |
| 1–2 years     | 18%              | 23%             | 18%             |                 |
| >2 years      | 12%              | 40%             | 21%             |                 |

*Diabetic retinopathy/age related macular degeneration.
‡Based on Govt of India census definitions.
functioning (0.2%) and visual symptoms (6.9%). Skewness values were low (range $-0.16$ to $+0.09$).

An examination of the reliability of the IND-VFQ33 showed good internal consistency and test-retest reliability (table 3). Cronbach’s alpha coefficients indicated high internal consistency for all scales; all values exceeded the minimum criterion of 0.70 for scales and every item in each scale passed the item-total criterion of $>0.40$. For test-retest reliability, Pearson’s correlation coefficients for all scales were $>0.90$ and satisfactorily passed the threshold requirement of 0.80. As correlation coefficients can be misleading when evaluating the relation between two measures, we also applied the Bland-Altman method. The plots showed no evidence of bias as most of the mean differences between the two measures were close to 0.

Construct validity was examined both within scale and in comparison with other measures. The IND-VFQ33 shows good internal consistency as demonstrated by high item-total correlations and high alpha coefficients (table 3), indicating that a single construct is being measured and that items can be combined to form summary scores. Analyses of intercorrelations between scales followed the expected pattern: all three scales are intercorrelated ($>0.65$). Construct validity was also assessed by comparison with other measures. The IND-VFQ33 shows moderate convergent validity when compared with visual acuity in the better eye, (correlations of between 0.50 to 0.57 for the three scales). Results for discriminant validity were mixed when judged against sociodemographic measures. Low correlations (all were $<0.15$) between the IND-VFQ33 and age and sex suggest that these variables do not influence responses. However, there was evidence that responses varied according to education level and whether the participants lived in urban/rural areas (correlations ranged from [0.33] to [0.58] for education and urban/rural). These differences remained after adjustment for other variables including eye condition. Table 4 shows means and tests of differences for IND-VFQ33 scores for each of the clinical groups and the normal comparison group. Multiple regression analyses controlling for age, sex, education, urban/rural, and caste were used to test differences. For each clinical condition, all scales differentiated significantly between patients in the three clinical conditions and normal controls, providing support for construct validity.

<table>
<thead>
<tr>
<th>Condition</th>
<th>No</th>
<th>Mean (SD)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>General functioning (score range 21–105)‡</td>
<td>Cataract</td>
<td>359</td>
<td>65.90 (17.85)</td>
</tr>
<tr>
<td></td>
<td>Glaucoma</td>
<td>101</td>
<td>34.42 (13.81)</td>
</tr>
<tr>
<td></td>
<td>DR/AMD†</td>
<td>104</td>
<td>47.69 (16.49)</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>110</td>
<td>24.19 (3.81)</td>
</tr>
<tr>
<td>Psychosocial impact (score range 5–20)‡</td>
<td>Cataract</td>
<td>389</td>
<td>14.39 (4.63)</td>
</tr>
<tr>
<td></td>
<td>Glaucoma</td>
<td>116</td>
<td>8.21 (2.58)</td>
</tr>
<tr>
<td></td>
<td>DR/AMD†</td>
<td>120</td>
<td>10.92 (4.23)</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>118</td>
<td>5.56 (1.04)</td>
</tr>
<tr>
<td>Visual symptoms (score range 7–28)‡</td>
<td>Cataract</td>
<td>415</td>
<td>21.55 (4.59)</td>
</tr>
<tr>
<td></td>
<td>Glaucoma</td>
<td>116</td>
<td>13.67 (4.63)</td>
</tr>
<tr>
<td></td>
<td>DR/AMD†</td>
<td>120</td>
<td>17.17 (5.05)</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>118</td>
<td>9.27 (2.80)</td>
</tr>
</tbody>
</table>

*Analyses controlling for age, sex, area, education, caste.
†p Values for tests of differences between conditions in the model.
‡High scores indicate poorer quality of life.
§Diabetic retinopathy/age related macular degeneration.
**Table 6  Indian vision function questionnaire (33 item)**

In the first section, I am going to ask you how much your vision problem affects you in doing your daily activities. I will read out a choice of four answers and you will choose the one you feel describes you best. If you cannot do, or don’t do this activity because of vision, or other reasons, please tell me.

<table>
<thead>
<tr>
<th>Question Number</th>
<th>General functioning scale</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>A lot</th>
<th>Cannot do this because of my sight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Because of your vision how much problem do you have in climbing stairs?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Because of your vision how much problem do you have in making out the bumps and holes in the road when walking?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Because of your vision how much problem do you have in seeing if there are animals or vehicles when walking?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Because of your vision how much problem do you have in finding your way in new places?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Because of your vision how much problem do you have in going to social functions such as weddings?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Because of your vision how much problem do you have in going out at night?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Because of your vision how much problem do you have in finding your way indoors?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Because of your vision how much problem do you have in seeing the steps of the bus when climbing in or out?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Because of your vision how much problem do you have in recognising people from a distance?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Because of your vision how much problem do you have in recognising the face of a person standing near you?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Because of your vision how much problem do you have in locking or unlocking the door?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Because of your vision how much problem do you have in doing your usual work either in the house or outside?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Because of your vision how much problem do you have in doing your work up to your usual standard?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Because of your vision how much problem do you have in searching for things at home?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Because of your vision how much problem do you have in seeing outside in bright sunlight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Because of your vision how much problem do you have in seeing when coming into the house after being in the sunlight?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Because of your vision how much problem do you have in seeing differences in colours?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Because of your vision how much problem do you have in making out differences in coins or notes?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Because of your vision how much problem do you have in going to the toilet?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Because of your vision how much problem do you have in seeing objects that may have fallen in the food?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Because of your vision how much problem do you have in seeing the level in the container when pouring?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IND-VFQ33 scores showed improvements after surgery, indicating good responsiveness (table 5). Effect sizes are large (all exceed 1.00) and are similar to those reported in the MIOLS study for the group receiving IOL surgery.4

**DISCUSSION**

The Indian vision function questionnaire 33 item questionnaire (IND-VFQ33) (table 6) directly captures patients’ experiences of their vision problems upon their daily lives. Questionnaire items are classified into one of three scales (general functioning, psychosocial impact, and visual symptoms). Developed as an interviewer administered questionnaire and taking an average 20–25 minutes to complete, the IND-VFQ33 is suitable for use in populations of mixed literacy levels and short enough to keep respondent burden to a minimum. Subsequent psychometric evaluation found the IND-VFQ33 to be an acceptable, reliable, valid, and responsive measure of vision function.

Although the IND-VFQ33 shows satisfactory psychometric properties, there are a number of caveats to consider when evaluating the psychometric evidence. Firstly, as the test-retest interval for determining instrument reliability was 1–2 days, respondents’ recall of their answers from the initial questionnaire administration may have led to over-estimate of test-retest reliability.

Secondly, although the IND-VFQ33 demonstrated good convergent validity when compared to measures of visual acuity and, importantly, distinguished between people with different types of eye problems including those with no eye problems, we were unable to undertake a head to head comparison with other measures of quality of life because of the limited availability of such questionnaires validated for use in India. Future evaluation should include a comparison with the vision related quality of life instrument developed for use in the MIOLS study—bearing in mind that unlike the IND-VFQ33, the latter is based solely on expert opinion rather than new qualitative data from patients. It is also advisable to control for education and urban/rural effects in IND-VFQ33 data analyses because responses appear to be influenced by these factors.

Thirdly, the IND-VFQ33 produces separate summary scores for the three scales rather than an overall total score. This is because it is methodologically unsound to simply sum raw scores in a questionnaire such as the IND-VFQ, which includes items with a varying number of response scale options. Yet in order to make direct comparisons of the three summary scores when the IND-VFQ33 is used in future studies, and for ease of interpretation, it would be appropriate to standardise the three summary scores to a common 100 point scale to produce a summary score. Future research with IND-VFQ33 could consider the feasibility of creating an overall total summary score using formal methods of standardised scores such as z score equivalents.

Fourthly, instrument responsiveness was confined to cataract patients because cataract surgery provides a clearly defined treatment intervention of known efficacy which the instrument should and did detect. There is scope to evaluate the responsiveness of IND-VFQ33 in other clinical conditions (for example, refractive error).

Fifthly, the IND-VFQ33 is an interviewer administered questionnaire. Great care was taken in our study to train and monitor interviewers in the principles and conduct of questionnaire administration. Potential users of the questionnaire should therefore also be aware of the importance of interviewer training and quality assurance.

Finally, it is envisaged that IND-VFQ33, which has been shown to be a practical and scientifically sound measure, will be used to evaluate vision related quality of life in clinical trials, epidemiological studies, or clinical audit throughout India and possibly south Asia, where social, cultural, and
lifestyle factors may be more similar than different. As with other instruments measuring vision related quality of life,\textsuperscript{14,15} it is likely that future research efforts will refine the IND-VFQ33. Any subsequent modifications to the IND-VFQ33, including changes in format, content, or translation into other languages, would need to be re-evaluated for psychometric properties in an independent sample.

**ACKNOWLEDGEMENTS**

We would like to thank the participants who took part in this study, and the following people and organisations.

---

**Authors’ affiliations**

S K Gupta, G V S Murthy, Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India

K Viswanath, Sarojini Devi Eye Hospital, Hyderabad, India

R D Thulasiraj, Lions Aravind Institute of Community Ophthalmology, Madurai, India

D L Lamping, S C Smith, M Donoghue, A E Fletcher, London School of Hygiene and Tropical Medicine, London, UK

This study was funded by the US-India Fund via the US Embassy, New Delhi, India.

Data access and responsibility: Drs GVS Murthy and Dr SK Gupta had full access to all the data in the study and take responsibility for the integrity of the data and the data analysis.

Study staff at each centre: Dr Rajendra Prasad Centre for Ophthalmic Sciences: Professor HK Tewari, Professor VK Dada (Emeritus), Dr Lalit Sanga, Zakia Sultan, Akhillesh Kumar, Kiran Singh, Neena John, Hira Ballabh Pant, KG Varghese, Priska Kujur, Naveen Bhatt, RP Pathak, Rakesh Tewari, and Kamal Kishor: Aravind Eye Hospital: Dr Dipankar Dutta, Preethi Pradhan, V Vijaykumar, R Janakeeswari, Ms Manimeghalai: Sarojini Devi Eye Hospital: Dr R Praveen Krishna, D Sunitha Bhat, S Anitha, K Bala Saraswathi Kumari, Mr Ramesh, Kiran Didugu.

The technical advisory committee: Dr Leon B Ellwein (Committee Chair), Associate Director, National Eye Institute, National Institutes of Health, Building 31, Room 6A51, 31 Center Drive, Bethesda, MD, USA; Dr Damodar Bachani, Assistant Director General (Ophthalmology), Directorate General of Health Services, Government of India, New Delhi; Dr Paul Lee, Professor of Ophthalmology, Duke University Medical Centre, USA; Dr Carol Mangione, Professor of Medicine, David Geffen School of Medicine UCLA, Los Angeles, USA; Dr Rhett Schiffman, former director of uveitis services and clinical research, Henry Ford Health Systems, Detroit, USA (currently at Allergan, Inc).

---

**REFERENCES**


www.bjophthalmol.com
Bacterial endophthalmitis is one of the most serious complications following intraocular operations and penetrating ocular trauma. In the first setting the commonest micro-organisms involved are either Gram positive (Staphylococcus epidermidis, Staphylococcus aureus, streptococci, Propionibacterium acnes) or Gram negative (Pseudomonas aeruginosa, Haemophilus influenzae, and Serratia marcescens) while in post-traumatic endophthalmitis there is significant involvement of Bacillus cereus and Staphylococcus aureus.1

Systemically administered antibiotics have to penetrate the existing blood-ocular barriers in order to reach therapeutic intraocular levels. Although there is evidence from studies in humans and rabbits that intraocular penetration of systemic antibiotics is higher in inflamed eyes,2,4 there are other facts complicating this issue. Most of the antibiotics used have to be administered intravenously at frequent intervals, thus compromising the need of an antibiotic to reach levels in the anterior chamber much higher than the minimal inhibitory concentrations (MICs) in order to eliminate the microorganisms potentially inoculated during surgery. Among previously studied systemic antibiotics, fluoroquinolones and, in particular ciprofloxacin, ofloxacin, and levofloxacin (all of which can be administered orally), have been found to have significant penetration into aqueous humour and less so into the vitreous body, with concentrations usually exceeding MICs of pathogens implicated in intraocular infections.5,6 Ciprofloxacin and ofloxacin are second generation fluoroquinolones while levofloxacin comprises the third generation of these drugs.

The aim of our study was to determine the ocular penetration of moxifloxacin, a new generation fluoroquinolone, in the anterior chamber of the human uninflamed eye.

**Aims:** To determine the pharmacokinetics of moxifloxacin, a new generation fluoroquinolone, in the anterior chamber of the human uninflamed eye.

**Methods:** 35 patients undergoing cataract surgery received two doses of 400 mg of oral moxifloxacin with a 12 hour interval and were divided into six groups. Moxifloxacin levels in aqueous humour and serum were determined by a microbiological agar well diffusion technique at 2, 4, 6, 8, 10, and 12 hours after the second dose in each group respectively.

**Results:** Mean moxifloxacin levels in the anterior chamber were 1.20 (SD 0.35) µg/ml at the 2 hours group, 1.22 (0.48) µg/ml at the 4 hours group, 1.20 (0.45) µg/ml at the 6 hours group, 1.58 (0.38) µg/ml at the 8 hours group, 1.37 (0.44) µg/ml at the 10 hours group, and 1.23 (0.55) µg/ml at the 12 hours group. The mean ratio of aqueous to serum moxifloxacin level was 38%.

**Conclusion:** Moxifloxacin penetrates well into the anterior chamber of the human uninflamed eye after oral administration, reaching early significant levels, which are maintained for at least 12 hours and are much higher than the MIC<sub>90</sub> values of Gram positive and Gram negative pathogens commonly implicated in intraocular infections with the exceptions of fluoroquinolone resistant staphylococci, MRSA, and Pseudomonas aeruginosa.


**Abbreviations:** MIC, minimal inhibitory concentration; MRSA, methicillin resistant Staphylococcus aureus
cases within 4 weeks of sampling. Antibiotic level assays were performed using a microbiological agar well diffusion technique using Mueller-Hinton agar test as medium and *B. subtilis* ATCC 6633 as indicator micro-organism. High performance liquid chromatography (HPLC) which is now a days widely used as a method of choice to assay drug levels, was not available in our laboratory at the time of the study, but the two dimension microbiological agar well assay used (if well designed and performed) has been proved to be sensitive and in excellent agreement with other techniques (immunological, HPLC).

**RESULTS**

Of the 35 participants in this study 14 were male and 21 female. Their age ranged from 50–87 years (mean 73 years). Common underlying systemic diseases included hypertension, diabetes mellitus, hyperlipidaemia, and cardiovascular diseases, all of them well controlled at the time of surgery. In all cases the indication for surgery was visually significant cataract. In only one case was cataract secondary (steroid induced in a patient with scleroderma). Five of the 35 patients had glaucoma that was controlled with only topical medication. Four patients with glaucoma received oral acetazolamide before the operation to lower intraocular pressure further, depending on preoperative measurements. The acetazolamide dose was 250 mg administered orally approximately 2 hours before surgery. The administration of acetazolamide did not seem to affect the penetration of moxifloxacin into the aqueous humour in these patients (data not shown). Diabetes also did not affect the penetration of moxifloxacin and levels achieved were comparable between diabetic (10 patients) and not diabetic patients (data not shown).

There were no side effects from moxifloxacin administration in the patients enrolled in the study.

Moxifloxacin levels in aqueous and serum for all patient groups (expressed as mean values (SD)) are shown in table 1. The average concentration of moxifloxacin in aqueous humour ranged between 1.2 µg/ml (2, 4, 6, and 12 hours after the second dose) and 1.58 µg/ml (8 hours after the second dose). In serum, the average concentration ranged between 2.29 µg/ml (12 hours after the second dose) and 4.86 µg/ml (4 hours after the second dose). Peak concentrations were recorded at 4 hours after the second dose in serum and 8 hours after dosing in aqueous. Figure 1 depicts the mean antibiotic concentrations over time in aqueous and serum. From these data it is evident that moxifloxacin concentrations reach significant levels fairly soon (2 hours) after the last dose of the antibiotic, that remain high during the following hours, showing stability over time. Interpatient variation was greater for serum values than in aqueous humour values, where the results were clustered around the mean for all groups as shown in figure 2. Mean ratio of aqueous humour levels to serum levels was 38%, ranging between 25% (2–4 hours after dosing) and 57% (8 hours after dosing).

**DISCUSSION**

Moxifloxacin is a new fourth generation fluoroquinolone with a broad spectrum of activity against Gram positive and

<table>
<thead>
<tr>
<th>Time from last dose to sampling (hours)</th>
<th>Average moxifloxacin levels in serum (µg/ml)</th>
<th>Average moxifloxacin levels in aqueous (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (6 patients) 2</td>
<td>4.46 (1.62)</td>
<td>1.2 (0.35)</td>
</tr>
<tr>
<td>Group 2 (6 patients) 4</td>
<td>4.86 (2.95)</td>
<td>1.22 (0.48)</td>
</tr>
<tr>
<td>Group 3 (5 patients) 6</td>
<td>3.30 (1.21)</td>
<td>1.20 (0.45)</td>
</tr>
<tr>
<td>Group 4 (6 patients) 8</td>
<td>2.79 (1.03)</td>
<td>1.58 (0.38)</td>
</tr>
<tr>
<td>Group 5 (6 patients) 10</td>
<td>2.77 (1.23)</td>
<td>1.37 (0.44)</td>
</tr>
<tr>
<td>Group 6 (6 patients) 12</td>
<td>2.59 (1.42)</td>
<td>1.23 (0.55)</td>
</tr>
</tbody>
</table>

*Table 1 Mean moxifloxacin levels with their standard deviations in serum and aqueous humour for all groups*
Gram negative micro-organisms. In a recent study moxifloxacin was found to be the most potent fluoroquinolone for Gram positive bacteria (including methicillin resistant Staphylococcus aureus (MRSA) and ciprofloxacin resistant Staphylococcus aureus) and equally potent as other fluoroquinolones against Gram negative bacteria, with the exception of P aeruginosa against which ciprofloxacin remains the most potent fluoroquinolone. An advantage of moxifloxacin is its wide spectrum of activity: it is especially very potent against Gram positive bacteria, which are the cause of the vast majority of cases of endophthalmitis. Median MIC\textsubscript{90} values of moxifloxacin against common pathogens are shown in table 2, where it is evident that the drug exhibits excellent in vitro activity against an array of micro-organisms commonly encountered in bacterial endophthalmitis, except fluoroquinolone resistant Staph aureus. Moxifloxacin levels in serum were in agreement with those of previous studies. The median ratio of aqueous to serum levels was 38% and was significantly higher than the values obtained with other fluoroquinolones (15–23% for ciprofloxacin, 23% for ofloxacin, 13–23% for levofloxacin and 21.02% for gatifloxacin depending on the total dose). This finding confirms that moxifloxacin has very good penetration in the aqueous humour through the intact blood-ocular barriers in the uninflamed eye. The Endophthalmitis Vitrectomy Study showed no benefit of the use of systemic antibiotics in terms of final visual acuity in cases of endophthalmitis after cataract surgery or secondary lens implantation (antibiotics used were cefazidine and amikacin). In any endophthalmitis case from any cause, as well as in prophylaxis of high risk eyes (for example, trauma), it would be advantageous for an antibiotic to reach such high levels intraocularly and for a sufficient duration of time in order to eliminate the most common pathogens encountered in these cases. New generation fluoroquinolones seem to be first line candidates for that indication. Moxifloxacin is especially very potent against Gram positive bacteria, which are the cause of the vast majority of cases of endophthalmitis. Median MIC\textsubscript{90} values of moxifloxacin against common pathogens are shown in table 2, where it is evident that the drug exhibits excellent in vitro activity against an array of micro-organisms commonly encountered in bacterial endophthalmitis, except fluoroquinolone resistant Staph aureus. Moxifloxacin levels in serum were in agreement with those of previous studies. The median ratio of aqueous to serum levels was 38% and was significantly higher than the values obtained with other fluoroquinolones (15–23% for ciprofloxacin, 23% for ofloxacin, 13–23% for levofloxacin and 21.02% for gatifloxacin depending on the total dose). This finding confirms that moxifloxacin has very good penetration in the aqueous humour through the intact blood-ocular barriers in the uninflamed eye. The Endophthalmitis Vitrectomy Study showed no benefit of the use of systemic antibiotics in terms of final visual acuity in cases of endophthalmitis after cataract surgery or secondary lens implantation (antibiotics used were cefazidine and amikacin). In any endophthalmitis case from any cause, as well as in prophylaxis of high risk eyes (for example, trauma), it would be advantageous for an antibiotic to reach such high levels intraocularly and for a sufficient duration of time in order to eliminate the most common pathogens encountered in these cases. New generation fluoroquinolones seem to be first line candidates for that indication.

### Table 2: The median minimum inhibitory concentrations (MIC\textsubscript{90}) of common pathogens to moxifloxacin

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Isolated in bacterial endophthalmitis cases (peak aqueous levels/MIC\textsubscript{90} (µg/ml))</th>
<th>Isolated in systemic infections (peak aqueous levels/MIC\textsubscript{90} (µg/ml))</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>0.12 (13.3)</td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus FQR</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus FQS</td>
<td>0.06 (26.6)</td>
<td></td>
</tr>
<tr>
<td>CoagNeg staphylococcus FQR</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>CoagNeg staphylococcus FQS</td>
<td>0.03 (32)</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>0.09 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>0.13 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>0.19 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Gram negatives</td>
<td>0.08 (20)</td>
<td>0.25 (6.4)</td>
</tr>
<tr>
<td>Bacillus species</td>
<td>0.09 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neisseria species</td>
<td>0.06 (26.6)</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

FQR, resistant to ciprofloxacin and ofloxacin as determined by disc diffusion; FQS, susceptible to ciprofloxacin and ofloxacin as determined by disc diffusion; Gram negatives, assortment of various Gram negative bacteria isolated from endophthalmitis cases (mainly Haemophilus sp and P aeruginosa). MSSA, methicillin sensitive Staphylococcus aureus; MRSA, methicillin resistant Staphylococcus aureus.
and are favoured because of the convenience of oral administration (although not ideal drugs for the rare cases of pseudomonal infections of the eye).

Prevention of the devastating results of intraocular infections justifies the interest and research in this era. Moxifloxacin, because of its easy way of administration, relative safety compared to other fourth generation quinolones (less QT prolongation, no effect on glycemic control), a broad antimicrobial spectrum, and very good penetration into the anterior chamber and steady levels as shown in our study, could be a valuable addition to our armamentarium in the prevention and treatment of bacterial endophthalmitis, and warrants further clinical investigation.

Authors’ affiliations
G Kampougeris, E Kavouklis, Department of Ophthalmology, Laiko General Hospital, Athens, Greece
A Antoniadou, Z Chryssouli, H Giamarellou, 4th Department of Internal Medicine, Athens University School of Medicine, Attikon University General Hospital, Athens, Greece

The authors have no proprietary interest in any of the antimicrobials mentioned in this manuscript.

REFERENCES
Corneal graft rejection occurs despite Fas ligand expression and apoptosis of infiltrating cells

K A Williams, S D Standfield, J R Smith, D J Coster

**Background/aims:** Constitutive expression of Fas ligand (CD95L) protects the eye against cell mediated immune responses by inducing apoptosis in infiltrating Fas bearing T cells. This study was designed to examine Fas ligand expression on acutely rejecting rat corneal grafts and to investigate the kinetics of induction of apoptosis in infiltrating leucocytes.

**Methods:** Orthotopic penetrating corneal transplantation was performed between genetically disparate inbred rats. Fas ligand expression and the phenotype of infiltrating leucocytes were examined by immunohistochemistry. Apoptotic nuclei were visualised in sections of normal rat cornea, rejecting allografts, and time matched isografts by terminal deoxynucleotidyl transferase mediated dUTP biotin nick end labelling (TUNEL) and quantified by video image analysis. Staining with Hoechst dye 33258 was used to confirm the presence of apoptotic nuclei.

**Results:** Fas ligand was expressed on corneal endothelial and epithelial cells during acute corneal graft rejection. At all time points examined, including as early as the fifth postoperative day, the cells infiltrating both corneal isografts and allografts were TUNEL positive. By the 15th postoperative day, over 90% of all nuclei, many of which were T cells, were apoptotic.

**Conclusion:** Expression of Fas ligand is not downregulated on the cornea during allograft rejection and infiltrating leucocytes in both isografts and allografts die rapidly in situ. Despite the death of the cells believed to be responsible for rejection, isografts survive indefinitely whereas allografts are irreparably damaged.
**Immunohistochemistry**

Polyclonal rabbit anti-rat CD95L (Fas ligand) antibodies (FAS-L (N-20) sc-834, detecting amino acids mapping to the amino terminus of rat CD95L; FAS-L (C-178) sc-6237, detecting amino acids mapping to the carboxy terminus of rat CD95L) (Santa Cruz Biotechnologies Inc, Santa Cruz, CA, USA) were used at 5 μg/ml. Heat inactivated normal rabbit serum diluted to 5 μg/ml immunoglobulin was used as the normal control. Grafted eyes were fixed 2–4 hours at 4°C in paraformaldehyde-hyamine-periodate solution,6 soaked for USA) were used at 5 μg/ml. Heat inactivated normal rat serum was used as the negative control. Grafted eyes were fixed 2–4 hours at 4°C in 7% weight/volume (w/v) sucrose in phosphate buffered saline (PBS; 150 mM NaCl, 6 mM Na2HPO4, 4 mM KH2PO4, pH 7.2) and subsequently for 6 hours in 15% w/v sucrose in PBS before snap freezing in liquid nitrogen. Sections cut at 8 μm on the cryostat were transferred to chrome-alum subbed slides and blocked in 10% volume/volume (v/v) heat inactivated normal swine serum (NSS; Trace Biosystems, Sydney, Australia) at room temperature (RT). They were incubated with primary antibody for 18 hours at RT and washed three times with PBS containing 0.2% w/v gelatin (Ajax, Auburn, Australia). Following incubation with biotinylated affinity isolated sheep anti-rabbit immunoglobulins (Silenus, Melbourne, Australia) diluted 1/100 in PBS containing 1% v/v heat inactivated normal rat serum, 1% heat inactivated NSS, and 1% heat inactivated fetal calf serum (FCS; Trace Biosystems, Sydney, Australia) for 18 hours at RT, sections were washed three times with PBS-gelatin and incubated with horseradish peroxidase conjugated streptavidin (Dako Corporation, Carpinteria, CA, USA) diluted 1/1000 in PBS for 30 minutes at RT, and washed three times in PBS-gelatin. The reaction product was developed for 5 minutes with a solution of 0.1 M TRIS-HCl buffer, pH 7.6, containing 0.3% w/v sodium azide, 0.6 mg/ml 3,3’ diaminobenzidine tetrahydrochloride (Sigma Chemical Company, St Louis, MO, USA), 10 mM imidazole, and 0.07% v/v hydrogen peroxide (Ajax, Auburn, Australia). Sections were counterstained with haematoxylin, dehydrated through graded alcohols to xylene and mounted in Depex (BDH, Poole, UK).

Immunohistochemistry using monoclonal antibodies on paraformaldehyde-hyamine-periodate fixed sections of grafted eyes was performed as described elsewhere.16 Monoclonal antibodies were undiluted culture supernatants from stationary phase murine hybridoma cultures obtained from the ECACC (Porton Down, Salisbury, Wiltshire, UK) unless otherwise specified. Isotype matched negative controls X63 (IgG1) and SAL5 (IgG2a) were the gift of Professor H Zola, Adelaide, Australia; OK18, an anti-MHC class I antibody, was the positive control. Specific antibodies included OX1, anti-CD45; OX35, OX38, W3/25, all anti-CD4; OX8, anti-CD8; NDS61, anti-IL-2R; OX42, anti-IC3b receptor (macrophage and granulocyte); ED1, anti-macrophage, monocyte, and some dendritic cells. Sections were counterstained with haematoxylin to allow nuclear morphology to be assessed. Staining was assessed at the light microscope using a semiquantitative scoring system as follows: − = no positively stained infiltrating cells; + = few positively stained infiltrating cells; ++ = moderate number of positively stained infiltrating cells; +++ = many positively stained infiltrating cells. Sections from two to three isografts and two to three allografts were examined at days 5, 7, 12, 14, 21, and 28 post-graft.

**Terminal deoxynucleotidyl transferase mediated dUTP biotin nick end labelling (TUNEL)**

TUNEL was performed according to a modification of a published method.20 Grafted rat eyes or lymph nodes from normal rats were removed post mortem, fixed in 4% buffered formalin for a minimum of 24 hours and paraffin embedded. Sections of 5 μm were adhered to slides precoated with a 1/50 dilution of Histogrip (Zymed, San Francisco, CA, USA) in acetone, deparaffinised, hydrated through graded alcohols to distilled water, and permeabilised with 4 μg/ml proteinase K (Merck, Darmstadt, Germany) for 10 minutes at RT. Nick end labelling was accomplished by incubating sections with 0.11 units/ml terminal deoxynucleotidyl transferase in pH 6.6 buffer containing 5 mM cobalt chloride, 200 mM potassium cacodylate, 25 mM TRIS-HCl, 250 μg/ml bovine serum albumin, 0.375 mM biotinylated deoxy-uridine triphosphate (dUTP), and 75 μM deoxy-adenosine triphosphate (all from Boehringer-Mannheim, Mannheim, Germany) for 60 minutes at 37°C. The reaction was terminated by washing in 0.6 M sodium chloride/0.06 M sodium citrate buffer for 15 minutes at RT, in PBS for 1 minute at RT, and in PBS containing 2% v/v FCS and 0.2% v/v Triton-X100 (Sigma, St Louis, MO, USA) for 30 minutes at RT. Non-specific binding sites were blocked with 10% heat inactivated NSS for 10 minutes at RT, and the sections were washed for 10 minutes with PBS-gelatin before endogenous peroxidase was blocked with 0.09% v/v H2O2 in methanol for 20 minutes at RT. Sections were washed three times with PBS-gelatin before 1/50 dilution of horseradish peroxidase conjugated streptavidin (Dako Corporation, Carpinteria, CA, USA) was incubated for 1 hour at RT, sections were washed three times with PBS-gelatin and incubated with horseradish peroxidase conjugated streptavidin (Dako Corporation, Carpinteria, CA, USA) diluted 1/1000 in PBS for 30 minutes at RT, and washed three times in PBS-gelatin. The reaction product was developed, counterstained, and mounted as described above. Negative control sections were stained identically, but with omission of biotinylated dUTP from the nick end labelling mixture.

**Video image analysis of TUNEL sections**

A whole sagittal section through the centre of each grafted cornea was examined. Sections were scanned at 200× magnification using a video image analysis system (Video-Pro 32; Leading Edge Pty Ltd, Adelaide, Australia). Images were captured using a Panasonic CCD video camera and digitised with a PV 100 16 bit colour video digitiser card in an Intel 80486 DX processor based personal computer. The digitised image was displayed on a SVGA monitor in a 640×480 pixel variable window with 21 bit resolution. Transmitted light intensity and stability of light output were standardised as described elsewhere.21 Video image analysis measurements were made of the total area stained blue (by haematoxylin) and brown (by the TUNEL chromogen product). The total number of haematoxylin stained cell nuclei (representing nuclei of corneal cells and infiltrating cells) in each field was determined using feature counting.

**Staining with Hoechst dye 33258**

Hoechst dye 33258 (bis-benzimidide; Sigma, St Louis, MO, USA) was used to visualise apoptotic nuclei.22 Rat thymus was teased apart with forceps in HEPES RPMI 1640 medium supplemented with 100 units/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine (all from ICN-Flow, Sydney, Australia) and 10% v/v heat inactivated FCS. The cell suspension was filtered through a sterile gauze, washed twice in medium and adjusted to 4×106 viable cells/ml. Equal volumes of cell suspension were incubated for 20 hours at 37°C with or without 1 mM dexamethasone (David Bull Laboratories, Melbourne, Australia). The cells were washed in medium, fixed for 10 minutes at RT in 2.6% v/v formaldehyde, 2% w/v glucose, and 0.005 M NaN3 in PBS, washed twice in distilled water, and adjusted to 5×106 cells/ml. A volume of 10 μl of cell suspension was smeared on a glass slide, allowed to air dry and stained with 10 μg/ml Hoechst dye 33258 in distilled water for 30 minutes at RT. The slides were washed twice in distilled water, air dried and mounted in 50% v/v glycerol in PBS. To prepare whole
mounts, rat corneas were excised at the limbus, immersed in the dye solution for 30 minutes at RT, washed twice by immersion in distilled water, and mounted in 50%v/v glycerol in PBS. Smears and whole mounts were examined under the fluorescence microscope at an excitation wavelength of 360–370 nm.

RESULTS

Fas ligand as detected by FAS-L (N20) was present on normal rat corneal epithelium and endothelium (fig 1). Similar expression was observed on rat corneal allografts harvested at 15 days post graft during acute rejection (fig 1). No down-regulation of Fas ligand was apparent: expression may have actually been upregulated. The same pattern of expression was seen with FAS-L (C-178) (data not shown).

Apoptotic nuclei in sections of rat tissue were visualised by TUNEL. Some positive staining of cells in the corneal epithelium of normal rat corneas was observed and occasional keratocytes and corneal endothelial cells were also positive (fig 2A). Many cells infiltrating rat corneal isografts (fig 2B) and the majority of cells infiltrating acutely rejecting allografts (fig 2D) were TUNEL positive. Apoptotic mononuclear cells were observed attached to the corneal endothelium. Some keratocytes also appeared TUNEL positive. No staining was observed in the controls in which biotinylated dUTP was omitted (fig 2C). Rat lymph node showed very few strongly TUNEL positive cells confined to germinal centres (fig 2E, F), thereby confirming that the strong positive staining observed in the corneal grafts was not non-specific staining of all leucocytes.

In a kinetic study, grafts were stained for TUNEL at postoperative day 0 (immediately post-graft), day 5 (when infiltrating cells were first observed in the grafted tissue), day 10 (early allograft rejection), day 15 (acute allograft rejection), day 21 (late allograft rejection), and (in the case of isografts only) more than 60 days (long surviving grafts). The percentages of TUNEL positive nuclei in the stroma of corneal allografts, time matched isografts, and normal control rat corneas were quantified by video image analysis (table 1). The striking increase in the percentage positivity observed with increasing time after transplantation in rejecting allografts primarily reflected the greater number of infiltrating mononuclear cells contributing to the total cell count at these times.

To confirm the TUNEL results using another method of detecting apoptotic nuclei, corneas were stained with Hoechst dye 33258. As a positive control, apoptosis was induced in a suspension of rat thymocytes by incubation with dexamethasone. After staining with Hoechst 33258, the preparation showed many small bright fragmented nuclei with condensed chromatin, typical of apoptotic figures (fig 3A). Comparison of normal rat corneas (fig 3B) and rejecting corneal allografts (fig 3C) similarly stained with Hoechst 33258 and examined as whole mounts showed numerous brightly staining nuclei with condensed chromatin in the stroma of the latter only.

Figure 1 Immunoperoxidase staining. (A) Normal rat corneal epithelium, negative control: normal rabbit serum, 5 μg/ml total immunoglobulin; (B) normal rat corneal endothelium and posterior stroma, negative control: normal rabbit serum, 5 μg/ml total immunoglobulin; (C) normal rat corneal epithelium, anti-Fas ligand (FAS-L (N20)), 5 μg/ml specific antibody; (D) normal rat corneal endothelium and posterior stroma, anti-Fas ligand (FAS-L (N20)), 5 μg/ml specific antibody; (E) corneal allograft, day 15 post-graft, negative control: normal rabbit serum, 5 μg/ml total immunoglobulin; (F) corneal allograft, day 15 post-graft, anti-Fas ligand (FAS-L (N20)), 5 μg/ml specific antibody. A light haematoxylin counterstain was applied to all sections; the dark brown staining represents diaminobenzidine reaction product.
To characterise more closely the phenotype of the TUNEL positive cells infiltrating isografts and allografts in this model, immunohistochemistry for rat leucocytic markers was performed on isografts and allografts at varying time points after graft (Table 2). No staining was observed with the negative control antibodies in any section and the positive control for TUNEL reaction (biotinylated dUTP omitted from reaction).

Table 1  Percentage of TUNEL positive nuclei in grafted rat corneas at various times after transplantation

<table>
<thead>
<tr>
<th>Specimen</th>
<th>No of eyes*</th>
<th>Mean (SD) % TUNEL + nuclei in corneal stroma without dUTP†</th>
<th>With dUTP‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal corneas</td>
<td>5</td>
<td>1.7 (2.3)</td>
<td>29.3 (15.3)</td>
</tr>
<tr>
<td>Isograft day 0</td>
<td>3</td>
<td>1.5 (3.1)</td>
<td>35.3 (17.6)</td>
</tr>
<tr>
<td>Isograft day 3</td>
<td>3</td>
<td>1.7 (2.7)</td>
<td>50.1 (19.2)</td>
</tr>
<tr>
<td>Isograft day 10</td>
<td>3</td>
<td>0.3 (0.8)</td>
<td>33.9 (14.8)</td>
</tr>
<tr>
<td>Isograft day 14</td>
<td>3</td>
<td>1.5 (1.4)</td>
<td>47.9 (28.8)</td>
</tr>
<tr>
<td>Isograft day 21</td>
<td>3</td>
<td>0.4 (0.9)</td>
<td>65.0 (22.8)</td>
</tr>
<tr>
<td>Isograft day &gt;60</td>
<td>4</td>
<td>0.9 (0.9)</td>
<td>42.5 (16.3)</td>
</tr>
<tr>
<td>Allograft day 0</td>
<td>3</td>
<td>2.1 (4.0)</td>
<td>29.2 (19.9)</td>
</tr>
<tr>
<td>Allograft day 5</td>
<td>3</td>
<td>2.4 (3.0)</td>
<td>57.8 (10.4)</td>
</tr>
<tr>
<td>Allograft day 10</td>
<td>3</td>
<td>0.8 (0.9)</td>
<td>75.3 (12.4)</td>
</tr>
<tr>
<td>Allograft day 15</td>
<td>3</td>
<td>8.4 (4.7)</td>
<td>93.6 (6.3)</td>
</tr>
<tr>
<td>Allograft day 21</td>
<td>3</td>
<td>0.8 (1.4)</td>
<td>78.3 (18.0)</td>
</tr>
</tbody>
</table>

*Only one eye of any rat was grafted for ethical reasons, therefore number of eyes represents number of rats.
†Control for TUNEL reaction (biotinylated dUTP omitted from reaction).
‡Test for TUNEL reaction (biotinylated dUTP included in reaction).
control antibody showed appropriate staining in all sections. In isografts, a few CD45 positive cells had moved into the graft by the fifth postoperative day, clustered primarily in the periphery around the graft sutures. These cells were predominantly granulocytes, macrophages, and/or dendritic cells as judged by positivity with OX42 and ED1. Cells bearing T cell markers were extremely rare in isografts at all times examined. No leucocytes were observed in the anterior chamber of isografts at any time. In allografts, an early infiltrate of granulocytes, macrophages, and/or dendritic cells at the graft-host junction was observed. At day 5 post-graft, there were more cells bearing the iC3b receptor in allografts than in isografts. T cells were already present in allografts at day 5 post-graft and increased in number in the central cornea during rejection. The influx of CD4 positive cells preceded the influx of CD8 positive cells by at least a week. CD4 positive cells were also found in the anterior chamber after 1 week, whereas CD8 positive cells were not noted until day 21. Small numbers of neutrophils were identified by their nuclear morphology in some allografts.

Dual immunoperoxidase and TUNEL staining on the same sections was not performed because of the different processing required for the two protocols. However, all sections were inspected at the light microscope to assess concordance of staining. As pointed out above, some corneal epithelial cells, and occasional keratocytes and corneal endothelial cells, were TUNEL positive and therefore presumably apoptotic. These cells were readily identifiable from their location and morphology and were apparent in normal corneas, isografts, and allografts. The cells infiltrating isografts were predominantly myeloid lineage cells with very sparse numbers of T cells, and were mostly TUNEL positive irrespective of phenotype. These same cells were also TUNEL positive in allografts but the majority of infiltrating cells, especially in the central areas of the grafts, were TUNEL positive T cells.

**DISCUSSION**

In normal rat cornea, Fas ligand was detected by immuno-histochemistry on epithelial and endothelial cells. Both mouse and human cornea have previously been shown to express Fas ligand constitutively, and thus our finding was not unexpected. However, the rejection rate of normal murine corneal grafts has been reported to be of the order of 45–47% across at common strain combinations. In contrast, approximately 85–100% of corneal grafts from WF donors to F344 recipients are rejected at a median of 16–17 days postoperatively without the need for deliberate prevascularisation of the recipient cornea. In the light of these differences, we hypothesised that Fas ligand might be significantly downregulated during acute corneal graft rejection in the rat, thereby allowing infiltrating T cells to survive and mediate rejection. However, in this model both epithelial and endothelial cells remained strongly positive for Fas ligand product as detected by two different antibodies against the amino and carboxy termini, respectively, of the molecule.

The expected result of expression of Fas ligand would be induction of apoptosis in Fas bearing infiltrating leucocytes (including CD4+ T cells, CD8+ T cells, neutrophils, and macrophages) as has already been shown in transplanted corneas in the mouse, and this was precisely what we observed. The TUNEL method was used to visualise apoptotic cells and was coupled with video image analysis for the quantification of the number of apoptotic nuclei. Normal rat corneas exhibited some positive TUNEL staining in epithelium, as has been reported previously. Occasional keratocytes and corneal endothelial cells were also TUNEL positive, but there was no leucocytic infiltrate in normal corneas. In contrast, isografts showed a slight cellular infiltrate of cells bearing myeloid lineage markers that were mostly localised to the area of the graft-host junction, whereas allografts showed a more marked, central infiltrate of leucocytes that were predominantly T cells. The identity and kinetics of infiltration of leucocytes in rat corneal isografts and allografts was essentially as has been described previously in our own and other laboratories. Virtually all infiltrating leucocytes in both isografts and allografts were apoptotic as judged by positive TUNEL staining.

We examined the time of appearance of apoptotic cells in rejecting orthotopic rat corneal grafts and in time matched isografts. Metalloproteinases have been reported to release human Fas ligand from the cell surface; the cleaved soluble Fas ligand is an inefficient trigger of apoptosis and instead may competitively inhibit membrane bound Fas ligand induced cell death. Furthermore, Fas ligand induced killing of T cells requires T cell receptor stimulation. We therefore suspected that there might be a brief time period during which infiltrating cells in allografts were TUNEL negative, perhaps through release of Fas ligand from the surface of corneal cells, and that the small number of T cells infiltrating isografts might not undergo apoptosis because their T cell receptors would not have been ligated by foreign antigen. However, cells infiltrating both isografts and allografts appeared to undergo apoptosis as soon as they interacted with corneal tissue, although the effect was more pronounced in the allografts. An infiltrate was first observed at the light microscope at about day 5 postoperatively and at

---

**Table 2** **Identity of cells infiltrating rat corneal isografts and allografts**

<table>
<thead>
<tr>
<th>Antibody specificity</th>
<th>Specimen</th>
<th>Cellular infiltrate at day post-graft</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>CD45</td>
<td>Isograft</td>
<td>+</td>
</tr>
<tr>
<td>CD4</td>
<td>Allograft</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Isograft</td>
<td>–/–</td>
</tr>
<tr>
<td></td>
<td>Allograft</td>
<td>+/-</td>
</tr>
<tr>
<td>CD8</td>
<td>Isograft</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Allograft</td>
<td>+/-</td>
</tr>
<tr>
<td>IL2R</td>
<td>Isograft</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Allograft</td>
<td>–</td>
</tr>
<tr>
<td>iC3bR</td>
<td>Isograft</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Allograft</td>
<td>++</td>
</tr>
<tr>
<td>ED1</td>
<td>Isograft</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Allograft</td>
<td>++</td>
</tr>
</tbody>
</table>

*2–3 eyes were examined per time point.
† = no positively stained infiltrating cells; + = few positively stained infiltrating cells; ++ = moderate number of positively stained infiltrating cells; +++ = many positively stained infiltrating cells.
this time point, the infiltrating cells were already TUNEL positive. We did not observe a window in which infiltrating cells were TUNEL negative: the increasing percentage of TUNEL positive nuclei observed with increasing time post-graft reflected a steady increase in the number of infiltrating leukocytes present in the corneal tissue. Modulators of apoptosis, such as Bcl-2 and various growth factors, are expressed by human corneal cells, in tissue sections and/or in culture. Expression of such modulators may be altered during corneal graft rejection, but not to the extent that apoptosis is blocked. TUNEL has been used previously to study apoptosis within the cornea, and we consider our staining technique to be reliable. Firstly, the negative controls (in which biotinylated dUTP was omitted) consistently showed minimal positive staining (table 1). Secondly, normal cornea showed the expected pattern of TUNEL positivity (primarily in basal epithelium), whereas normal rat lymph node was negative. Thirdly, apoptotic nuclei within allografts (but not normal corneas) were directly visualised by staining of corneal whole mounts with the nuclear dye Hoechst 33258, an independent test for condensed chromatin and apoptotic-like nuclear figures. Attempts to confirm the TUNEL staining by extracting DNA from rejecting corneal grafts and running the extracts on agarose gels produced inconsistent DNA laddering, because the small size of the grafts limited the amount of DNA available for extraction (data not shown).

Finally, induction of apoptosis in infiltrating Fas positive cells was entirely consistent with the observation that the cornea continued to express Fas ligand during the rejection process. Our data do not allow us to draw a causal link between Fas ligand expression and induction of apoptosis in cells infiltrating corneal grafts in the rat, but elegant experiments in which the occurrence of corneal allograft rejection was strongly enhanced when mutant Fas ligand negative (gld) were used as donors provide such evidence for the mouse and, by extension, for other species.

How, then, do corneal grafts undergo rejection? Corneal graft rejection appears histologically to be an inflammatory process with characteristics typical of a delayed type hypersensitivity response: the infiltrate is mixed, but is composed predominantly of T cells. In the non-inflammatory programmed cell death that occurs as part of normal development, apoptotic nuclei are quickly cleared by phagocytosis. TUNEL positive cells may accumulate in rejecting corneal grafts because there are insufficient phagocytic cells present in the grafts to clear the substantial number of dead and dying T cells. Although apoptosis is a rapid process, it may be that infiltrating T cells can kill their targets more quickly, so that “murder” precedes “suicide.” Alternatively, Sonoda and colleagues have shown that CD1d positive NKT cells can induce allosecretory regulatory T cells that may promote corneal graft survival. Should these cells be induced to undergo apoptosis early in the allorejection, then perhaps a crucial control mechanism may be abrogated.

It has been suggested that the “immunological privilege” enjoyed by the eye and the testis, two organs that express Fas ligand, is a result of low levels of Fas ligand expression and induction of apoptosis in cells infiltrating the grafts. In eyes that have been inflamed or where the cornea is vascularised, there is overwhelming evidence in a variety of species, including humans, to support the contention that rejection is the expected outcome for corneal grafts. Immune privilege in the eye is plainly relative and can be overcome, but the mechanism by which rejection occurs, given that so many of the cells presumed to be involved are dead, remains obscure.

ACKNOWLEDGEMENTS

The authors thank Mr R Yates for expert assistance with animal husbandry and Dr SL Wesselingh for advice on the TUNEL method.

REFERENCES

Disappearance of eyelid xanthelasma following oral simvastatin (Zocor)

The major risk factors for coronary heart disease include smoking, elevated blood pressure, and elevated serum cholesterol. Risk reduction starts with identification of those at risk and then alteration of factors such as discontinuation of smoking, lowering of blood pressure, and reduction of serum cholesterol. Patients who should have blood cholesterol testing include those with family history of premature coronary heart disease or hyperlipidaemia, personal history of coronary heart disease, or clinical evidence of elevated lipids with features of xanthelasma, corneal arcus under age 50 years, and cutaneous xanthomas at any age. Two of the latter clinical features are ophthalmic and detection relies on the ophthalmologist.

Xanthelasma appear as multiple yellow placoid lesions in the pericocular region and represent a concentration of lipocytes in the dermis. There are numerous methods to manage the cosmetic appearance of xanthelasma, which typically involves surgical excision or laser ablation. We report a novel approach to management using oral cholesterol lowering medication and patience.

Case report

In 1992, a 68 year old male smoker with a history of hypertension and elevated serum cholesterol was referred for evaluation of a newly diagnosed iris mass. On examination, the visual acuity was 20/20 in both eyes. The mass was diagnosed as a benign iris naevus and observation was advised. Coincidental bilateral upper and lower eyelid xanthelasma were detected (fig 1A). The largest xanthelasma measured 16 mm in diameter. Observation was advised with tentative plan for surgical excision in the future. The patient was advised to continue his antihypertensive medications and antihypertensive medication (oral simvastatin (Zocor) 20 mg once daily). At the 6 month follow up the iris naevus was stable and the xanthelasma persisted. Yearly examinations were advised. The patient did not return for 10 years. Surprisingly, the xanthelasma had completely resolved, leaving no clinical trace of subcutaneous lipid (fig 1B). He continued on his medications and serum cholesterol was normal.

Comment

In the Lipids Research Clinics Program Prevalence Study, xanthelasma and corneal arcus were associated with increased levels of serum cholesterol and low density lipoprotein cholesterol (LDL-C), especially in young men. People with either lesion had increased odds of having type IIa dyslipoproteinemia. Adjusted odds ratios for ischaemic heart disease in participants with xanthelasma and corneal arcus were generally increased. The study concluded that the clinical findings of xanthelasma or corneal arcus, especially in young people, helped to identify those with plasma lipoprotein abnormalities.

Management of patients with elevated LDL-C include both low cholesterol diet and cholesterol lowering medications, the most popular of which are the statins. There are currently five statin drugs on the market in the United States and these include lovastatin (Mevacor, Altocor), simvastatin (Zocor), pravastatin (Pravachol), fluvastatin (Lescol), and atorvastatin (Lipitor). The major effect of these medications is to lower LDL-C by slowing down the production of cholesterol and by increasing the liver’s ability to metabolise the LDL-C in the blood. Statins reduce LDL-C by approximately 40% and produce a modest increase in high density lipoprotein-cholesterol (HDL-C). These medications are given daily in the evening to take advantage of the fact that the body makes more cholesterol at night. Statins reduce measured blood LDL-C within 4-6 weeks. In a study of 20 536 patients, this resulted in long term reduction in coronary heart disease, stroke, and mortality.

Simvastatin is derived synthetically from a fermentation product of Aspergillus terreus. Simvastatin is hydrolysed to an inhibitor of an enzyme responsible for cholesterol synthesis. In the Multicenter Anti-Atheroma Study, simvastatin slowed the progression of atherosclerosis, measured by vascular stenosis diameter on angiography, and decreased significantly the development of new lesions.

To our knowledge, there have been no previous reports on the effect of statins on eyelid xanthelasma. A PubMed search for keywords “statin and xanthelasma” and simvastatin and xanthelasma yielded no relevant publications. The management of eyelid xanthelasma includes surgical excision, microsurgical inverted peeling, laser inverted peeling, resurfacing, photodynamic using carbon dioxide laser, and application of bichloracetic acid. Patients with the highest recurrence rate are those with elevated cholesterol. These local treatments do not address possible systemic associations. By observations in this report, we suggest that serum cholesterol be evaluated and if elevated, oral statin combined with dietary cholesterol restriction might result in resolution of xanthelasma over time, but, more importantly, reduction of patient cardiac risk.

C L Shields, A Mashayekhi, J A Shields
Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, USA

P Racciato
Pocono Medical Center, Stroudsburg, PA, USA

Correspondence to: Carol L Shields, MD, Ocular Oncology Service, Wills Eye Hospital, 840 Walnut Street, Philadelphia, PA 19107, USA; carol.shields@shieldsoc.com

doi: 10.1136/bjo.2004.053058

Accepted for publication 13 September 2004

References


www.bjophthalmol.com
New onset diplopia: 14 years after retinal detachment surgery with a hydrogel scleral buckle

In 1979, the hydrogel explant (Miragel, Waltham, MA, USA) was introduced as a scleral buckling material in the surgical management of retinal detachment. It was widely used in the 1980s and early 1990s as it was initially believed to be well tolerated, less prone to infection, and easy to manipulate. However, long term complications related to swelling and fragmentation of the explant have been reported over recent years, resulting in discontinuation of its use in 1999.

Case report

A 36 year old healthy man presented on 2003 with symptoms of mild right ocular discomfort. Past ocular history included a right retinal detachment repair 14 years previously, using a 907 (3 x 5 mm) Miragel scleral buckle (Miragel, Medical Instruments Research Associates, Waltham, MA, USA), sutured to the inferior sclera. On examination, visual acuity was 20/120 right and 20/20 left. There was no diplopia or limitation of eye movements. What was thought to be a small conjunctival cyst was noted inferiorly but, otherwise, the ocular examination was unremarkable and the retina was secure.

A year later (2004), he presented with increasing marked right ocular discomfort and diplopia in all fields. His visual acuity was unchanged, but there was marked restriction of elevation and reduction in adduction of the right eye and binocular swelling in all fields of gaze. A tense swelling of the inferior conjunctiva was noted (fig 1, top), intraocular pressure was normal, and the retina was flat with a moderate anterior buckle effect. Computed tomography (CT) (fig 1, bottom) demonstrated a right orbital circumferential soft tissue mass surrounding lower half of the globe with a small area of calcification on the inferotemporal sclera.

In our case, there was a profound increase in the explant volume during a 14 year period. The resulting diplopia and restriction of extraocular movement as well as the clinical evaluation mimicked a giant orbital inclusion cyst. The correct diagnosis was only made intraoperatively. Scleral thinning and necrosis as seen in our case has been reported previously, resulting in intraoperative vitreous leak after removal of the expanded explant. In our patient, there was an area of thinned sclera, but the surrounding calcification and the early removal of the explant prevented vitreous leak.

It is important to note that patients who have undergone scleral buckling with hydrogel explants before 1995 are at risk of developing this complication. Symptoms of progressive diplopia, pain, and restriction of extraocular muscle movement in these patients should also raise the possibility of explant expansion. The assistance of a retinal surgeon may sometimes be required because of the increased risk of scleral thinning and leakage of liquid vitreous intraoperatively.

References


Invasive globe retraction syndrome complicating recurrent pterygium

Often larger and more aggressive than the original lesion, recurrent pterygia can cause visual symptoms that are most often secondary to their mechanical effects on the cornea. We report a case of invasive globe retraction syndrome (that is, retraction during abdication) due to the restrictive effect of a recurrent pterygium and the management of this complication.

Case report

A 28 year old man without a medical history or ocular symptoms underwent pterygium excision in his left eye with a superotemporal conjunctival autograft and intraoperative mitomycin C. Three weeks postoperatively, he noted a feeling of pressure in the left eye
The patient’s appearance 6 weeks after amniotic membrane placement in (A) primary gaze, (B) right gaze, (C) left gaze. There is no longer globe retraction left eye during left gaze. During right gaze, abduction in the left eye occurs with less effort than abduction in the right eye.

Comment
Inverse globe retraction syndrome is rare. It has been reported as being caused by medial rectus abnormality,1 innervational misdirection,2 and secondary to restriction from traumatic tissue capture in the medial orbital wall. The current case demonstrates another cause for the syndrome, globe restriction as a result of a leash effect from aggressive pterygium recurrence. The risk of pterygium recurrence after initial pterygium removal is minimised by the technique of conjunctival autograft with adjunctive mitomycin C; however, because aggressive recurrence is still possible initial pterygium surgery should only be performed for patients with significant cosmetic and/or functional concerns. For the management of inverse globe retraction syndrome complicating recurrent pterygium in this case, the use of amniotic membrane as a tissue spacer permitted excellent functional improvement.

Figure 1 The patient’s appearance at presentation in (A) primary gaze, (B) right gaze, (C) left gaze. There is relative enophthalmos in the left eye that increases during left gaze. During right gaze, abduction in the left eye occurs with less effort than abduction in the right eye.

Figure 2 The patient’s appearance 6 weeks after amniotic membrane placement in (A) primary gaze, (B) right gaze, (C) left gaze. There is no longer globe retraction left eye during left gaze. During right gaze, abduction in the left eye occurs with effort similar to that needed for abduction in the right eye.

References

Seeing is not believing
We describe a case of posterior cortical atrophy presenting with progressive visuoperceptual and visuospatial difficulties, but with no abnormalities on standard ophthalmological examination.

Case report
The patient, a 53 year old right handed woman, with well controlled primary generalised epilepsy, presented to her optometrist with a 1 year history of deterioration in vision. She had particular difficulties with walking downstairs and following text while reading. She could read 6/12+2 RE (with −0.75/−0.25 × 90 correction) and 6/12+3 (with −0.75 × 90 correction) LE. With +2.25 correction she could read N5 slowly with each eye. On subsequent ophthalmological review no significant abnormality was found on examination and no specific diagnosis was made.

Over the following months her vision deteriorated. She reported difficulties following a line while writing and was unable to tell when a glass was full when pouring a drink. Her husband thought that she was unable to see things in her peripheral vision. This culminated in her crashing her car. She did not have any memory difficulties, she had preserved insight, and there had been no change in personality.

On admission to our unit her visual acuity was 6/18 RE and 6/12 LE with the above correction. She was able to read slowly at N5 corrected with each eye but was unable to name any of the Ishihara plate numbers including the test plate, despite being able to name the colours, trace the outline of the numbers with her finger, and read numbers in normal print. Confrontation visual fields were essentially full although she was slow to recognise objects in her peripheral visual fields owing to an apparent narrowing of attention to foveal vision and had optic ataxia, in that she was unable to localise in space, by pointing, objects placed in her peripheral visual fields. On Goldmann perimeter her visual fields appeared somewhat constricted, probably related to her difficulties with attention, but, importantly, no hemianopia was demonstrated (fig 1).

Pupillary responses were normal as was fundal examination. On eye movement testing she had broken smooth pursuit eye movements, although she was able to generate voluntary saccades. The rest of the neurological examination was unremarkable.

Her mini-mental state examination score was 28/30. She had some deficits in verbal abstract reasoning and made occasional phonemic errors in speech. She had mild dyscalculia and dyspraxia, but she was able to differentiate left from right and name body parts. She had mild memory impairment, although these were mainly in tasks requiring visual input. She demonstrated simultagnosia in that she was unable to see the whole of a picture and only described parts of it.

On testing with the cortical vision screening test she passed the hue discrimination test, the word reading test, face perception test, the crowding test of letter reading and was able to detect the presence of a circle in the shape detection test but was unsure what to say if it was not present. On the symbol
any of the Ishihara plates, with otherwise slow, near vision. Her inability to recognise visuospatial ability, given her good, albeit acuity may have been related to her poor cognitive deficits. Her poor distance visual diagnosis of posterior cortical atrophy was made.

parietal and occipital lobes (fig 2). A diagnosis most marked in the both posterior sections to indicate right parietal dysfunction.

screening tests for higher visual function deficits can then be employed.\(^1\)\(^2\)\(^3\)

The corollary of this is that a patient with an established diagnosis of dementia should be tested for disorders of higher visual function, because a patient with otherwise mild cognitive deficits may still be driving.\(^4\)

S J Hickman, D Alvares, H Crewes, R J Wise, A N Gale
Royal Free Hospital, Pond Street, London NW3 2QG, UK

Correspondence to: Simon J Hickman, Royal Free Hospital, Pond Street, London NW3 2QG, UK; simonhickman@btinternet.com
doi: 10.1136/bjo.2004.054429
Accepted for publication 28 September 2004

References


Radial optic neurotomy in combined cilioretinal artery and central retinal vein occlusion

Combined cilioretinal artery and central retinal vein occlusion (CRVO) is a rare condition first described by Oosterhuis.\(^7\) The pathogenesis of this condition is not well established and remains controversial. Most reports postulate that the initial CRVO causes an elevation of the intraluminal capillary pressure and induces a consecutively reduced perfusion pressure at the arterial side. Since the perfusion pressure of the cilioretinal artery is lower than the central artery, it becomes relatively occluded.\(^8\) Recently Opremcak et al described radial optic neurotomy (RON) involving pars plana vitrectomy (PPV) and radial incision of the optic nerve to treat CRVO.\(^5\) We report this new surgical approach in a patient with combined cilioretinal artery occlusion and CRVO.

Case report

A healthy 64 year old woman complained of unilaterally blurred vision for the past 3 days. Her visual acuity (VA) was 20/200 in the right eye (RE) and 20/20 in the left eye (LE). The anterior segment in both eyes was unremarkable on slit lamp examination. Fundus examination RE demonstrated a whitening of the macula corresponding to an area supplied by a cilioretinal artery. The retinal veins were dilated, accompanied by adjacent retinal haemorrhages (fig 1A). The fundus of the left eye appeared normal. Fluorescein angiography (FA) RE revealed a delayed arteriovenous (AV) perfusion time of 13 seconds. Systemic evaluation of the patient did not reveal any general disease. Although treated systemically with corticosteroids\(^9\) and low dose heparin for 4 weeks, she developed CRVO with severe disc oedema, extensive dilatation of the retinal veins, radial orientated intraretinal haemorrhages, and cotton wool spots (fig 1B). On FA there was a reduced perfusion time of the cilioretinal artery in addition to the typical patients,\(^9\) although difficulty with figure-ground discrimination cannot be excluded.

Posterior cortical atrophy is a clinical and radiological diagnosis based upon the presence of occipitoparietal abnormalities with initially preserved occipitotemporal (face and colour recognition) and anterior cerebral function.\(^9\) It is thought to be as a result of Alzheimer’s disease, in most cases,\(^9\) although the syndrome has been described with other pathologies—for example, subcortical gliosis, Creutzfeld-Jakob disease, and progressive multifocal leukoencephalopathy.\(^9\) Although it is rare, it should be suspected in any patient presenting with visuoperceptual or visuospatial difficulties in the absence of any signs on standard ophthalmological examination. Screening tests for higher visual function deficits can then be employed.\(^9\)

Simultanagnosia and optic ataxia

This woman therefore presented with progressive visuoperceptual and visuospatial difficulties, but had no abnormalities on ophthalmological examination. She had some features of Balint’s syndrome (that is, simultanagnosia and optic ataxia)\(^9\) and other cognitive deficits. Her poor distance visual acuity may have been related to her poor visuospatial ability, given her good, albeit slow, near vision. Her inability to recognise any of the Ishihara plates, with otherwise normal colour vision, is probably a reflection of her other visuoperceptual difficulties, which has been reported before in similar
signs of CRVO (fig 2A). Based on positive results of RON in CRVO, we offered this treatment to our patient. After she signed an informed consent, RON was performed with two radial cuts at the nasal edge of the optic disc. After 2 days disc oedema was significantly reduced with sharp visible disc margins. Two months postoperatively the retinal haemorrhages, cotton wool spots, and disc oedema had blurred out and her VA improved to 20/25 RE (fig 1C). FA demonstrated a physiological AV perfusion time of less than 3 seconds and no signs of an occluded cilioretinal artery (fig 2B).

Comment

Combined cilioretinal artery occlusion and CRVO are discussed as a separate clinical entity in the literature,4,13 and its treatment by RON has not been described. Opremcak et al postulated that a surgical decompression of the optic disc and scleral ring by RON may contribute to an improved venous perfusion in CRVO. Our patient demonstrated additional signs of an arterial occlusion with delayed filling of the cilioretinal artery in the macula, which may induce permanent functional loss. The underlying pathomechanism of CRVO remain unknown, current discussion leans towards an intraluminal occlusion by a thrombus, increased extravasal pressure, or a combination of both as possible causes.7 In addition the therapeutic effect of RON is also questionable. It remains unclear as to whether RON causes a decompression of the optic disc increasing the ocular blood flow or induces the formation of new chorioretinal shunt vessel.8 In our case the goal of RON was to reduce the capillary pressure, therefore increasing the perfusion in the cilioretinal artery and thus improving central vision. Patients with combined occlusive AV disease may benefit from RON by improving their haemodynamic perfusion pressure, retinal anatomy, and consecutive central visual function.

5 Mennel, K Droutsas, C H Meyer, J C Schmidt, P Kroll
Department of Ophthalmology, Philipps-University Marburg, Germany

Correspondence to: Stefan Mennel, MD, Department of Ophthalmology, Philipps-University Marburg-Robert-Koch-Strasse 4, 35037 Marburg, Germany; stefan.mennel@lycos.com
doi: 10.1136/bjo.2004.054858
Accepted for publication 20 October 2004

Financial support: none.
Proprietary interest: none.

References


Value based medicine

In a fine recent editorial, Drs Melissa and Gary Brown raised issues at the nexus of health policy and clinical science.1 As utility assessment is relatively new to the visual sciences, understanding both the assumptions behind this work and the consequences of relaxing those assumptions is essential for the conduct of high quality research and appropriate interpretation of the results. The use of community elicited utilities (that is, including people without the disease in the elicitation study) in economic evaluation should be given more than minimal consideration. Metaeconomic evaluations are intended to inform health policy makers by assessing the value society places on the cure or prevention of disease. Community based utilities typically reflect larger estimates of utility loss than those elicited from patients and result in a more favourable analysis of the cost-effectiveness of preventive interventions than those relying on patient elicited utilities.2 At the same time, estimating community elicited utilities requires the development of easily understood scenarios to assist community members in understanding life with the disease.3 Following investigators prefer to rely on patient elicited utilities. Rather than dismiss the community elicited approach, economic evaluation in ophthalmology would be greatly facilitated by development of a catalogue of community elicited utilities related to old disease developed through the standard gamble or time trade-off methods or responses to health status questionnaires that include algorithms to estimate health utilities.

While the Browns caution against the use of functionally based health related quality of life instruments (for example, the NEI-VFI) in economic evaluation, we would like to offer an alternative explanation for this concern. Most disease specific instruments are based in psychometric theory and designed to measure change in the patient’s self reported health status in investigator defined domains.4 Domain scores do not reflect the importance the respondent assigns to the activities, but scoring algorithms developed by the instrument designer. The result is a metric that is often meaningful to clinicians but does not reflect the value the patient or society places on the health state. This limits generalisability across disease groups, as well as investigators’ ability to comment on the most efficient method to screen for, or treat, an ophthalmic condition affecting multiple areas of physical, mental, or emotional function.

Finally, the standard gamble elicitation method should not be dismissed off handedly. More frequent use of the time trade-off reflects the method’s intuitive appeal rather than theoretical superiority. As opposed to the time trade-off in which the anchor event (typically, death, blindness, etc.) occurs immediately, in the standard gamble the event is immediate. This provides an estimate of the person’s risk preference unconfounded by time. The time trade-off consistently results in higher estimates of utility loss than the standard gamble,5 potentially resulting in an overestimation of the cost-effectiveness of treatment or prevention.

We hope that our comments will help future work to be pragmatic and technically sound. This is necessary if we are to properly characterise the appropriateness of our methods as well as the value of our findings.

5 M Kymes
Washington University School of Medicine, Department of Ophthalmology and Visual Sciences, 660 South Euclid, Campus Box 8096, Saint Louis, MO 63116, USA

K D Frick
Johns Hopkins Bloomberg School of Public Health Department of Health Policy and Management, Baltimore, MD, USA

Correspondence to: Dr Steven Kymes, Washington University School of Medicine Department of Ophthalmology and Visual Sciences, 660 South Euclid, Campus Box 8096, Saint Louis, MO 63116, USA; kymes@vrcc.wustl.edu
doi: 10.1136/bjo.2004.063784
Accepted for publication 3 December 2004

www.bjophthalmol.com
We thank Drs Kymes and Frick for their excellent letter regarding utility analysis as a health related quality of life instrument. We agree that the use of primarily function based quality of life instruments such as the NEI-VFQ-25 may result in missing many important variables in the quality of life arena, as well as limit applicability across all diseases. In contrast, preference based quality of life instruments, such as utility analysis, are applicable across all diseases and encompass all variables that comprise quality of life, as well as the weighting of those variables. Of great additional importance is the fact that preference based instruments can be used in healthcare economic analyses, especially utility analysis. To our knowledge, such preference based instruments have not been successfully used.

Concerning the use of time trade-off and standard gamble utility analysis, we have found that the time trade-off methodology is easier for patients to comprehend and also is more sensitive to milder health states since there is risk aversion to the consequence of immediate death associated with the standard gamble method. Froberg and Kane have also shown that the time-trade-off method of utility has greater test-retest reliability, intra-rater reliability and inter-rater reliability than standard gamble methodology. In our experience, time trade-off utilities generally demonstrate better construct validity and a wider range between pre-intervention and post-intervention values than standard gamble utilities, thus resulting in more favourable cost utility analysis, rather then less favourable analyses.

With regard to quality of life respondents, we remain firm in our adherence to the fact that a basic pillar of value based medicine is the use of utility values obtained from respondents with a health state in question. We have found that utility value diminution in patients who actually have age related macular degeneration ranges from 10% to 75% greater than the decrement estimated by treating ophthalmologists for the same condition. This has been noted as well for non-ophthalmological health states.

We agree that community utility values generally overestimate the degree to which a disease decreases quality of life. In contrast, we and others have noted that community and provider participants asked to evaluate the quality of life associated with a health state using utility analysis generally underestimate the decrement in quality of life compared to patients with that health state. In essence, patients who have lived with a health state are those best able to ascertain the quality of life associated with that health state. And it is usually worse than others imagine.

In conclusion, we thank Kymes and Frick for their interest and comments and look forward to additional awareness in the arena of value based medicine. As increasing numbers of those who allocate healthcare resources become aware that value based medicine allows for higher quality care (by incorporating quality of life parameters that evidence based primary clinical trials often ignore) and the more efficient use of resources, it will have a considerably greater role in the delivery of cost effective, quality healthcare. When that takes place, all will benefit.

References

Authors’ reply
We thank Drs Kymes and Frick for their excellent letter regarding utility analysis as a health related quality of life instrument. We agree that the use of primarily function based quality of life instruments such as the NEI-VFQ-25 may result in missing many important variables in the quality of life arena, as well as limit applicability across all diseases. In contrast, preference based quality of life instruments, such as utility analysis, are applicable across all diseases and encompass all variables that comprise quality of life, as well as the weighting of those variables. Of great additional importance is the fact that preference based instruments can be used in healthcare economic analyses, especially utility analysis. To our knowledge, such preference based instruments have not been successfully used.

Concerning the use of time trade-off and standard gamble utility analysis, we have found that the time trade-off methodology is easier for patients to comprehend and also is more sensitive to milder health states since there is risk aversion to the consequence of immediate death associated with the standard gamble method. Froberg and Kane have also shown that the time-trade-off method of utility has greater test-retest reliability, intra-rater reliability and inter-rater reliability than standard gamble methodology. In our experience, time trade-off utilities generally demonstrate better construct validity and a wider range between pre-intervention and post-intervention values than standard gamble utilities, thus resulting in more favourable cost utility analysis, rather then less favourable analyses.

With regard to quality of life respondents, we remain firm in our adherence to the fact that a basic pillar of value based medicine is the use of utility values obtained from respondents with a health state in question. We have found that utility value diminution in patients who actually have age related macular degeneration ranges from 10% to 75% greater than the decrement estimated by treating ophthalmologists for the same condition. This has been noted as well for non-ophthalmological health states.

We agree that community utility values generally overestimate the degree to which a disease decreases quality of life. In contrast, we and others have noted that community and provider participants asked to evaluate the quality of life associated with a health state using utility analysis generally underestimate the decrement in quality of life compared to patients with that health state. In essence, patients who have lived with a health state are those best able to ascertain the quality of life associated with that health state. And it is usually worse than others imagine.

In conclusion, we thank Kymes and Frick for their interest and comments and look forward to additional awareness in the arena of value based medicine. As increasing numbers of those who allocate healthcare resources become aware that value based medicine allows for higher quality care (by incorporating quality of life parameters that evidence based primary clinical trials often ignore) and the more efficient use of resources, it will have a considerably greater role in the delivery of cost effective, quality healthcare. When that takes place, all will benefit.

References

Cystoid macular oedema with trypan blue use
We read with interest the article by Gonws et al. on the apparent increased incidence of cystoid macular oedema (CME) in phaco-emulsification patients when trypan blue was used to stain the anterior capsule. Trypan blue has been commonly used in both anterior and posterior segment surgeries. If trypan blue does cause macular toxicity, its risk should theoretically be higher when used in posterior segment surgeries. However, studies on the use of trypan blue, both in the anterior and posterior segments, did not show apparent toxicity. Thus, it would be appreciated if the authors could clarify whether other potential confounders were assessed in their study, including: (1) other causes of CMO such as diabetes, uveitis, and prostaglandin use; (2) operating time since phototoxicity from the operating microscope is a risk factor for CMO development. It appears that only operations for patients in group B were performed by one surgeon, if operations for patients in group A (with trypan blue use) were done by trainees, the operative time is expected to be longer; (3) whether all patients received a fundus examination with dilated pupil after the operation. If these were only performed in patients with suboptimal visual acuities, the incidence of CMO may be underestimated.

Finally, we concur with the authors’ view that we should try all means in terms of minimising any theoretical toxicities of trypan blue. It is our routine to actively remove trypan blue with the binimal irrigation aspiration system as soon as the anterior capsule has been stained. It is very effective and the potential toxicities may be reduced.

Authors’ reply
We thank Lam et al. for their interest. In response to their comments, as stated in the article and demonstrated in figures 1B and C, the effect persists when co-morbidity such as diabetes is removed.

Both groups’ surgery was performed by the same surgeon who did not have juniors attached to the list. Not all patients had dilated fundus examination postoperatively. Clinically significant cystoid macular oedema (CMO) is unlikely in a patient with visual acuity of 6/12 or better, although subclinical CMO can be demonstrated in up to 20% with fluorescein angiography.

References
This retrospective study on a unique cohort of patients provided us with the opportunity to demonstrate a potential side effect with the use of trypan blue. A prospective trial is required to control for all the variables and confirm or refute our findings.

P Gouws, P Simcock
Conquest Hospital, Hastings, UK

Correspondence to: Peter Simcock, West of England Eye Unit, Royal Devon and Exeter Hospital, Exeter EX2
SDW, UK; psimcock@hotmail.com
doi: 10.1136/bjo.2004.069765
Accepted for publication 23 February 2005

Reference
1999;25:1492–7

BOOK REVIEW

The History of Moorfields Eye Hospital, Volume III


Like John Mortimer’s book of a similar title this third volume of the history of Moorfields Eye Hospital is an affectionate but critical look back at the hospital that has been a major influence in many ophthalmologists’ training and subsequent practice. The volume is written in a positive upbeat style but also describes some of the faults and difficulties that have beset it in the past four decades. In a complex organisation such as a hospital there are inevitable inefficiencies and problems with personalities but the author has wisely stuck to the facts and has plotted the course of the management of the hospital in a very readable way; he has sensibly avoided petty confrontations and offers a lucid outline of the course of Britain’s flagship ophthalmic hospital.

The two previous histories of Moorfields described times past when ophthalmic practice changed only gradually and political upheaval was minor. The current author has been in the unique position of being involved with Moorfields throughout the 40 years he describes. Given the turmoil, both professional and managerial, that has engulfed the delivery of health care during this period he was fortunate that many of the individuals involved with the hospital were available for interview, thus providing first hand accounts of the good and bad times that affected the hospital. The various chapters outline lucidly the clinical and political changes of the time; Moorfields represents in microcosm all the influences to which NHS consultants of all disciplines have been subjected. One special feature of the period described is that it also covers the first 40 years following the foundation of the Institute of Ophthalmology and the not always easy relationship between the hospital and the institute is recorded both openly and tactfully.

The book comprises a number of chapters outlining the various aspects of the hospital development—for example, clinical, managerial, financial, etc. The first chapter is an overview involving all aspects of the hospital during the 40 years from 1963 to 2003. It provides a concise synopsis of all the forces bearing on the hospital; not only clinical but also in terms of research, teaching, and political upheaval. Indeed, for those younger ophthalmologists entering the profession at the present time this chapter gives a concise overview of those political influences that have shaped the lives of the NHS and its staff during recent decades.

As the author points out in his preface the subsequent chapters take up the issues raised in the first chapter and analyse them in more detail. If one, therefore, picks up the book and reads it cover to cover there is a strong author’s intention that the book should be necessarily read in this way. Each of the later chapters is written in a stand alone fashion dealing with clinical progress, academic development, research, management, and finance so that some repetition is inevitable. The major characters in the story of Moorfields development are given due weight; particularly Professor Barrie Jones, under whose influence Moorfields progressed from a rather slow moving organisation to the establishment of all the subspecialist services we know today.

Apart from rather a large number of nautical metaphors such as “calm waters,” “stormy seas,” and a few petty errors of detail, such as dates, this volume is a good read, particularly if approached as the author intended. He himself has made major contributions to the standing of Moorfields Eye Hospital and the book is written in the typically clear and polished style, reminiscent of his own scientific contributions.

R Grey
Bristol Eye Hospital, Lower Maudlin Street, Bristol BS1 2LX, UK; linda.clayton@uhbt.swest.nhs.uk

NOTICES

Worldwide clinical trials for new technique for early detection of eye disease

A unique new non-invasive technique for high resolution optical imaging of the eye is receiving global acclaim. By combining two high-resolution imaging technologies, the new technique provides doctors with 3-D images of the retina, macula and the optic nerve.

For more information, contact the Media Office on 01227 823581/823100 or email MediaOffice@kent.ac.uk. News releases can also be found at: http://www.kent.ac.uk/news

Trachoma control

The latest issue of Community Eye Health (No 52) discusses new developments in the control of trachoma. For further information please contact: Journal of Community Eye Health, International Resource Centre, International Centre for Eye Health, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (tel: +44 (0)20 7612 7964; email: Anita.Shahi@lshtm.ac.uk; online edition: www.jceh.co.uk). Annual subscription (4 issues) UK £28/US$45. Free to developing country applicants.

EVER 2005 meeting

This will take place on 5–8 October 2005 in Vilamoura, Portugal. For further details please contact: Christy Lacroix, EVER Secretary, Kapucijnenover 33, B-3000 Leuven, Belgium (tel: +32 (0)16 233 349; fax +32 (0)16 234 097; email:ever@skynet.be.).

World Ophthalmology Congress 2006 – Brazil

The World Ophthalmology Congress (which is replacing the International Congress of Ophthalmology) is meeting in February 2006 in Brazil. For further information on the congress and committees, scientific program and coordinators of different areas are available at the congress website www.ophthalmology2006.com.br

CORRECTIONS

In the letter entitled, Norrie disease and peripheral venous insufficiency (Br J Ophthalmol 2004;88:1475) the ordering of the authors was incorrect. The correct order is Michaelides M, Luthert PJ, Cooling R, Firth H, Moore AT. The journal apologises for this error.

doii: 10.1136/bjo.2005.58032corr1
“The combination of living in so many places with different people and attending so many different schools did not dislocate Nasser, it broadened his horizons—he got to know Egypt well. This meant becoming aware of the class divisions which raked it. Gamal travelled from one place to another by train, and he must have seen how inhumanely crowded the third-class compartments were and noted the conditions of the poor fellahin, or peasants who travelled in and even on top of them. Most fellahin travelled with all their earthly belongings gathered in one bundle which they carried on their backs, and most suffered from obvious eye and tooth disease. (Aburish, Said. Nasser. The Last Arab. London: Duckworth; 2004:10)

Diabetes mellitus develops spontaneously in middle aged obese rhesus monkeys, thus making them a good model for examining the effects of co-morbid factors on the development of end organ damage. Investigators from Johns Hopkins University have reported the structure and function in the eyes of one monkey who developed type 2 diabetes. The eyes showed intraretinal haemorrhages and large areas of retinal capillary non-perfusion. ICG angiography revealed a large area of non-perfused or poorly perfused choriocapillaris in one eye. Both basal laminar deposits and hard drusen were present on areas of Bruch’s membrane adjacent to non-viable choriocapillaris. Blood flow by the nasal posterior ciliary arteries to this section of choroid was not detectable by colour duplex Doppler ultrasound, indicating contribution of extraocular vascular disease to ischaemia in this eye. (Experimental Eye Research 2005;80:37-42)

Guidelines were originally published in 2002 for selection of patients for treatment with photodynamic therapy with verteporfin. Since 2002 additional information relevant to clinical care has been published. Revision to the 2002 guidelines on patient selection criteria include the following: (1) in cases due to age related macular degeneration, lesion composition of predominantly classic choroidal neovascularisation, or occult with no classic choroidal neovascularisation with presumed recent disease progression or relatively small minimally classic lesions, (2) classic choroidal neovascularisation location subfoveal or so close to the foveal centre that conventional laser photocogulation treatment almost certainly would extend under the centre, (3) aetiology of classic choroidal neovascularisation from age related macular degeneration, pathological myopia, or other causes in which the outcome without treatment is likely to be worse than with treatment; and (4) vision at a level where further loss would be recognised as detrimental to quality of life of the patient. (Retina 2005;25:119-34)

Although only 5% of those exposed to mycobacteria go on to develop acute tuberculosis, many have latent infections that have escaped antibiotic treatment and may recrudesce with stress or ageing. Investigators have recently tested a combined vaccine-chemotherapy regimen for its ability to prevent reactivation of disease in mice. Investigators made a DNA vaccine in a pgX10 vector containing two genes they had tested previously. In mice this vaccine coupled with isoniazid and pyrazinamide prevented reactivation of disease. (Gene Therapy 2005, 10.1038/sj.gt.3302465)

The National Cancer Institute is hoping to launch a $1.5 million effort to identify all major mutations in most human cancers. The 10 year project would gather tumour samples from thousands of patients. The goal to identify all mutations occurring at 5% frequency in the 50 most common types of cancer, would require 250 samples per type or 15 000 samples. The project would be jointly managed by MCI and the National Human Genome Research Institute. (Science 2005;307:1182)

The perception of surface albedo (lightness) is one of the most basic aspects of visual awareness. It is well known that apparent lightness of a target depends on the context in which it is embedded. Recent research suggests that the visual system explicitly separates surface reflectance from the prevailing illumination and atmospheric conditions in which it is embedded. Recent experiments suggest that mechanisms involved in decomposing images into layered representations can have a decisive role in the perception of surface lightness. (Nature 2005;434:79-82)

Elevated blood pressure is recognised as one of the risk factors for stroke. However, in a large prospective study of adults aged 45–73, 12% of strokes occurred in people with normal blood pressure. Multivaried analysis revealed that the other risk factors were older age, smoking, established heart disease, and increased body mass index. A new risk factor however emerged from this study: a history of gastric ulcer. More surprising was the finding that there was no relation between stroke and diabetes. (Stroke 2005;36:234-8)

It is well recognised that a significant proportion of patients who undergo coronary artery bypass have postoperative depression. The severity of this has now been highlighted by a study which suggests that the single most useful predictor of health status following coronary bypass is the presence or absence of depression. This was more important as a predictor than the age of the patient, history of previous heart attack or heart failure, diabetes, or left ventricular function. (Circulation 2005;111:271-7)

The risk of environmental tobacco smoke continues to be controversial. However, in a large study performed at Imperial College in London of more than 300 000 people who had never smoked or who have stopped smoking for at least 10 years, frequent exposure to environmental tobacco smoke during childhood was associated with lung cancer in adulthood. This study confirms that environmental tobacco smoke is a risk factor for lung cancer and other respiratory diseases, particularly in ex-smokers. (BMJ 2005;330:277-80)

Neuroscientists gathered at the University of Wisconsin in September to honour Ray Guilley and his work on the thalamus. The meeting focused on three research topics—presentations on the organisation and dynamic nature of the thalamocortical pathways, the role of the thalamus in communication between cortical areas, and the relation between sensory and motor pathways of the brain, including cognitive aspects of the thalamocortical processing. The conclusion of the meeting was that the communication between thalamus and cortex is so rich that one should no longer consider the operations of either structure separately from the other. (Neuron 2005;45:485–8)