Bevacizumab suppresses choroidal neovascularisation caused by pathological myopia

Bevacizumab (Avastin, Genentech) is a recombinant humanised, full length, anti-VEGF monoclonal antibody that binds all isoforms of VEGF-A. It has been shown to prolong survival of patients with advanced colon cancer when combined with 5-fluorouracil. In this report, we describe the effect of bevacizumab in two patients with choroidal neovascularisation (CNV) secondary to pathological myopia, which was refractory to other treatment.

Case reports

Patient 1

AM is a 36 year old white man who was diagnosed with subfoveal CNV caused by pathological myopia (right eye = −11.50 D, left eye = −11.50 D) in his left eye in September 2002 for which he received three photodynamic therapy (PDT) treatments. He developed subfoveal CNV in his right eye in June 2003 and received one PDT treatment combined with an intravitreous injection of 4 mg of triamcinolone acetonide. In May 2004, he presented with recurrent subfoveal CNV in his right eye and refused PDT. Off-label use of bevacizumab was discussed and after informed consent, the patient decided to proceed.

Just before treatment in July 2004, best corrected visual acuity (VA) was 20/40 in the right eye and 20/25 in the left eye. There was a ring of hyperpigmentation centred on the fovea with a surrounding ring of subretinal blood and substantial subretinal fluid in the right eye (fig 1A). An optical coherence tomography (OCT) scan through the centre of the fovea confirmed the presence of extensive subretinal fluid (fig 1B, asterisks) with subretinal tissue in the centre of the fovea (arrowheads). An OCT map showed severe thickening and subretinal fluid throughout the centre of the macula (foveal thickness 510 μm, macular volume 9.29 mm³). In the left eye, there were pigmentary changes and no subretinal blood or fluid (foveal thickness, 201 μm). In the right eye, the early phase of a fluorescein angiography (FA) scan showed a central area of hyperfluorescence surrounded by blocked fluorescence from subretinal blood (fig 2A). Central fluorescence increased in the mid phase (fig 2B) and in the late phase the area of hyperfluorescence was larger with indistinct borders indicating leakage of dye into surrounding tissue (fig 2C).

The patient received an intravenous infusion of 5 mg/kg of bevacizumab, which he tolerated well. He noted subjective improvement in vision in both eyes within 7 days and 2 weeks after the infusion, VA was 20/20 in both eyes and biomicroscopy showed less subretinal fluid (fig 1C), confirmed by OCT (fig 1D, asterisk). Compared to the pre-infusion OCT, the retinal thickness map showed substantial improvement with a decrease in foveal thickness (330 μm from 510 μm) and macular volume (6.89 mm³ from 9.29 mm³). In the early phase of a FA in the right eye (fig 2D), the hyperfluorescent area was reduced compared to a corresponding frame of the baseline FA (fig 2A). The intensity of hyperfluorescence increased between the early and mid phase (fig 2E) and there was evidence of dye leakage from the CNV during the late phase (fig 2F). The patient received second and third infusions of 5 mg/kg of bevacizumab without any difficulty. Six weeks after the first infusion and just before the fourth infusion, VA was 20/20 in each eye and biomicroscopy showed no identifiable subretinal fluid in the right eye and resorption of almost all of the subretinal blood (fig 1E). OCT confirmed that there was no subretinal fluid (fig 1F) and the retinal thickness map showed further improvement compared to the map after the first infusion. Foveal thickness measured 244 μm and macular volume was 5.80 mm³. Early phase of the FA showed further reduction in the area of hyperfluorescence (fig 2G) compared to a corresponding frame of the FA done after the first infusion (fig 2D). There was only a mild increase in brightness of the hyperfluorescent area in the mid phase of the FA.
Macular volume was 5.91 mm$^3$. There was PostScript 1369 (asterisk). Foveal thickness was 296 m and macular volume was 6.40 mm$^3$. In the right eye, there was a laser scar between the disc and the nasal border of the fovea. There were flecks of subretinal haemorrhage and mild subretinal fluid. In the left eye there was hypopigmentation with subretinal fluid, blood, and thickening in the macula (fig 3A). OCT in the left eye showed prominent retinal thickening surrounding a small central area of retinal atrophy (fig 3B, arrow). The retinal thickness map showed the thickest region of the retina to be located on the inferotemporal side of the fovea. Foveal thickness was 311 μm and macular volume was 7.30 mm$^3$. In the right eye, OCT showed retinal thinning in the region of the laser scar inferonasal to the fovea (fig 3C, arrows), and thickening superotemporal to the fovea with a pocket of subretinal fluid (asterisk). Foveal thickness was 296 μm and macular volume was 5.91 mm$^3$. There was subfoveal CNV in both eyes, and it was decided to transit the left eye because there was more retinal thickening in the left eye. The early phase of the FA showed a central area of hyperfluorescence and surrounding blocked fluorescence from subretinal blood (fig 4A). The hyperfluorescence became much brighter during the mid phase of the FA (fig 4B) and leaked during the late phase (fig 4C). The patient refused additional PDT and after careful consideration of potential risks and benefits and signing a consent form, the patient was given four intravenous infusions of 5 mg/kg of bevacizumab at intervals of 2 weeks, which she tolerated well.

Examination before the fourth infusion showed a VA of 20/64 in the right eye and 20/200 in the left eye. Biomicroscopy in the left eye showed reduced subretinal blood compared to the baseline examination, but persistent macular thickening (fig 3D) confirmed by OCT, which showed a foveal thickness of 304 μm and a macular volume of 7.37 mm$^3$. In the right eye, there was mild residual subretinal fluid and a few flecks of subretinal blood temporal to the laser scar. OCT in the right eye showed reduced retinal thickening and minimal subretinal fluid with foveal thickness of 249 μm and a macular volume of 5.78 mm$^3$ (fig 3F). In the left eye, early phase of a FA (fig 4D) showed a similar area of hyperfluorescence as that seen in the early phase of the baseline FA (fig 4A), but substantially less fluorescence during the mid (fig 4E) and late (fig 4F) phases than the corresponding phases of the baseline FA, indicating less filling of the CNV with dye. There was still substantial leakage of dye into surrounding tissue in the late phase (fig 4F). The patient returned 2 months after the fourth infusion noting subjective visual improvement that had allowed her to resume many activities that she had previously stopped. VA was 20/64 in the right eye and 20/200 in the left. Contact lens biomicroscopy in the left eye showed no identifiable subretinal blood or fluid, and macular thickness appeared reduced (fig 3G). This was confirmed by OCT (fig 3H; foveal thickness 233 μm, macular volume 6.40 mm$^3$). In the right eye, there was no identifiable subretinal blood or fluid and OCT showed no changes from the scan at week 6. FA in the left eye showed reduced hyperfluorescence compared to previous FAs at all phases, early (fig 4G), mid (fig 4H), and late (fig 4I), and no leakage.

**Comment**

In two patients, intravenous infusions of bevacizumab resulted in reduced fluorescein angiographic evidence of leakage from CNV and decreased retinal thickening and subretinal fluid. This anatomical evidence of
improvement was accompanied by visual improvement in two of the three eyes in which there was active subfoveal CNV at baseline. The one eye that did not show objective evidence of visual improvement had prominent subretinal fibrosis and a central area of retinal atrophy at baseline. Although spontaneous improvement cannot be ruled out, the possibility that the course of these two patients suggests that antagonism of VEGF with bevacizumab provided benefit. No ocular or systemic side effects were observed. Recent studies have suggested that VEGF may be an important stimulus for neovascular age-related macular degeneration (AMD). Despite differences in pathogenesis among the disease processes, the effect of bevacizumab in the two patients reported here suggests that VEGF may be an important stimulus for CNV in pathological myopia as well as AMD. While uncontrolled observations in two patients do not justify widespread use of bevacizumab in patients with CNV, additional studies are warranted. A controlled clinical trial is needed to determine if bevacizumab is safe and effective in patients with subfoveal CNV caused by pathological myopia, and if so, to determine the appropriate frequency of administration.

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References


Methods

One hundred consecutive patients using topical medication to lower intraocular pressure attending a UK teaching hospital's glaucoma service clinics were asked which drops they were using and how often they put them in. Each patient was only entered into the study once. If any deviation from the drop regime described in their notes was identified then further questioning was used to identify the cause of that discrepancy.

Results

In total, 30 of the 100 patients were not using the antiglaucoma medication as described in their notes. Eighteen cases were caused by ophthalmologists either changing a regime without informing the general practitioner or not giving clear instructions to the patient. Examples include transcription errors by the ophthalmologist when dictating the letter to the general practitioner (four cases), patients stopping treatments because of side effects without contacting clinic (four cases), patients stopping their bevacizumab drops after cataract surgery (three cases), and ambiguity between Xalatan and Xalacom (one case).

Patient error can be attributed to nine cases. Examples include patient using drops less frequently than prescribed (three cases), patient using drops in the wrong eye or one eye only (two cases), patients changing the dose frequency of their own accord (one case), and using drops too frequently (one case).

The other three cases were the result of "unreliable" nursing home staff (two cases), and failure to prescribe eye drops on admission to a general medical ward.

Compliance: clear communication's critical

Non-compliance can be subdivided into voluntary and involuntary types. Voluntary non-compliance is patients deciding not to use their medication. Involuntary non-compliance refers to situations where medications are used incorrectly, such as eye drops missing the conjunctival sac, using incorrect medication, or following an incorrect regime. The impact of non-compliance is particularly important for patients with chronic diseases such as glaucoma.

We collected data from patients in our clinic to try to ascertain the frequency and nature of any discrepancies between the drop regimes patients were using and what their notes said their current regimes should be.

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References


Safety of phacoemulsification in a patient with an implanted deep brain neurostimulation device

A 69 year old woman with nuclear sclerotic cataracts was examined. She was awaiting neurosurgery for treatment of drug refractory titubation (head tremor). Before cataract surgery, she underwent successful neurosurgery. The implanted Medtronic deep brain stimulation device rendered her asymptomatic of tremors. At the cataract preoperative clinic she showed the device identification card that stated “ultrasound diathermy ... anywhere on your body ... can result in severe injury or death.” Following confirmation from Medtronic that it was safe to proceed, the patient had an evenunait left phacoemulsification performed under general anaesthesia with the neurostimulator turned “off.” Seven months later she underwent a similar successful right phacoemulsification.

Comment

Deep brain neurostimulation of the thalamus is the treatment of choice for drug refractory essential tremor. Indications for its use are widening and include use in multiple sclerosis, advanced Parkinson’s disease, and movement disorders such as dystonia. The deep brain neurostimulator has three implanted components. The electrodes are implanted into the subthalamic nucleus or the globus pallidus interna, then an insulated lead is placed subcutaneously from the burr hole to a sealed neurostimulator device beneath the clavicle. The neurostimulator electrical stimulation pulses can be adjusted from external devices.

There are two recorded fatalities in patients with implanted deep brain neurostimulation devices. The implanted Medtronic deep brain stimulation device rendered her asymptomatic of tremors. At the cataract preoperative clinic she showed the device identification card that stated “ultrasound diathermy ... anywhere on your body ... can result in severe injury or death.” Following confirmation from Medtronic that it was safe to proceed, the patient had an evenunait left phacoemulsification performed under general anaesthesia with the neurostimulator turned “off.” Seven months later she underwent a similar successful right phacoemulsification.

Figure 1 Implanted deep brain neurostimulation device.
devices who had received short wave diathermy "as used by physiotherapists." Medtronic also report two similar patients who were still comatose. Another report described permanent, severe central nervous system injury following stimulation of a spinal cord neurostimulator by a radiofrequency antitheft device.

Brain damage results from heating of the implanted electrodes. Heat energy released directly to the body from an external source can be conducted via the insulated lead of an implanted neurostimulation device, raising the temperature at the electrode. Furthermore, if an external source generates an electric current in the insulated lead, this will result in a rise in the temperature at the electrode. Ultrasound diathermy transfers heat directly to the body where short wave diathermy results in an induced electrical current. One study calculated a potential risk of 9.7°C at the deep brain neurostimulator electrode when short wave diathermy was used. For phacoemulsification to be safe in patients with deep brain neurostimulators, it must not produce significant heat or generate an electric current.

The phacoemulsification hand piece uses the piezoelectric effect to drive the phacoemulsification needle tip in a linear jackhammer-like movement, physically cutting the lens. Acoustic cavitation results from an explosive collapse of vacuoles formed in fluid around the swiftly moving phacoemulsification needle tip. A study showed a maximum temperature rise of 3.5°C in the anterior chamber during routine phacoemulsification. The risk of this generated heat spreading to the implanted electrodes must be low. The phacoemulsification needle tip does not generate an oscillating magnetic field that might induce an electrical current. Theoretically, this should render ultrasound phacoemulsification safe in the presence of implanted deep brain neurostimulators.

With expanding technology, there will naturally be situations with the potential for interactions between equipment from different specialties. Consent should include the possibility of heat conduction to the implanted neurostimulation device. The use of local anaesthesia may allow early detection of discomfort or neurological sequelae. The surgeon should make use of all techniques to reduce the heat generated during phacoemulsification. Medtronic advise turning the neurostimulator off and not placing any cables over the patient’s chest and neck (R Coffey, 3 February 2005, personal communication). There are various neurostimulators, including cortical devices, that may have increased sensitivity to localised temperature increases. Heat formation at the phacoemulsification needle tip has been analysed; however, further research on the extent of heat dissipation is required.

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References

Vertical deviation exacerbated by convergence and accommodation
We report a patient with hypertropia causing diplopia exacerbated by convergence and accommodation.

Table 1 Angle of deviation on fixation at distance and near measured with the alternating prism cover test

<table>
<thead>
<tr>
<th>Distance</th>
<th>6 metres</th>
<th>6 metres with –1D lens</th>
<th>6 metres with –2D lens</th>
<th>6 metres with –3D lens</th>
<th>33 cm</th>
<th>33 cm with –3D lens</th>
<th>33 cm with 10 prism dioptr base-in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>0</td>
<td>–1 12 L/R</td>
<td>–2 24 L/R</td>
<td>–3 25 L/R</td>
<td>14 L/R</td>
<td>10 prism dioptr base-in</td>
<td>15 prism dioptr L/R</td>
</tr>
<tr>
<td>Right</td>
<td>0</td>
<td>12 L/R</td>
<td>24 L/R</td>
<td>25 L/R</td>
<td>14 L/R</td>
<td>10 prism dioptr base-in</td>
<td>15 prism dioptr L/R</td>
</tr>
<tr>
<td></td>
<td>left</td>
<td>right</td>
<td>left</td>
<td>right</td>
<td>left</td>
<td>right</td>
<td>left</td>
</tr>
</tbody>
</table>

Note: *Left over right*

Table 2 Harms Wall measurements in nine directions of gaze (upper panel) and head tilt to the right and left in primary position (lower panel) with left fixation

<table>
<thead>
<tr>
<th>Left fixation</th>
<th>0</th>
<th>4 L/R</th>
<th>12 L/R</th>
<th>17 L/R</th>
<th>Right fixation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>+1</td>
<td>+2</td>
<td>+3</td>
<td>+4</td>
<td>+2</td>
</tr>
<tr>
<td>L tilt</td>
<td>9</td>
<td>L/ R</td>
<td>–7</td>
<td>–20</td>
<td>0</td>
</tr>
<tr>
<td>R tilt</td>
<td>14</td>
<td>9</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

For each direction of gaze the first number indicated the horizontal deviation (ie, 2 = 2 degrees esotropia), the second measurement indicates the vertical deviation (ie, 14 L/R = 14 degrees left over right) and the number under the horizontal and vertical measurements indicated the cyclodeviation (ie, 0 = no cyclodeviation, 2 int = 2 degrees incyclotropia, 2 ex = 2 degrees excyclotropia).

Case report
A 36 year old man presented with 8 year history of worsening intermittent double vision. Visual acuities were 6/5 in each eye. For near there was manifest left hypertropia and left hyperphoria at distance (fig 1A, table 1). Extracular movements were full with no overactions. No significant difference in vertical deviation in different gaze positions or cycloptoria was found, the deviation increased on head tilt to the left (table 2). There was no dissociated vertical deviation. The angle of deviation varied between 2 and 7 prism dioptr at distance and 24 and 45 prism dioptr at near on repeated examinations. Stereovision was 55 seconds of arc when deviation was prism correct. The A/C A ratio was normal using gradient method. The vertical fusion range was 13 prism dioptr at distance (9 prism dioptr base-down and 4 prism dioptr base-up).

The vertical deviation increased on accommodation with concave lenses and the deviation decreased with 10 dioptre base-in prisms at near (table 1). Eye movement recordings are shown in figure 1C. Pupil reactions and fundoscopy were unremarkable. Thyroid functions, thyroid peroxidase and acetylcholine receptor antibodies were normal. Tension test was negative. Orbicularis oculi muscle single fibre electromyogram was unremarkable. Neurological examination and magnetic resonance imaging of the brain and orbits were normal.

Comment
Klein-Scharff and Kommerell first reported three patients with hypotropia and two with
hypotropia modulated by accommodation and/or convergence. In contrast with our patient, +3 dioptre lenses reduced the vertical deviation at near in at least one case. They concluded that the patient had vertical accommodative vergence. Four of five of their cases had additional forms of strabismus.

Graf and Weinand described a case of left hyperphoria increasing on convergence. Use of convex lenses and concave lenses did not change the vertical deviation. Similar to our patient, this child had an increase in vertical deviation when the head was tilted to the side of the hyperphoria/tropia. Graf has recently attributed this to the unidirectional fusalional vertical vergence tonus that develops to compensate for the vertical deviation. Graf described three additional cases with vertical accommodative vergence with hypotropia. As in our patients concave lenses at distant fixation increased the vertical deviation. Subsequently, a series of 19 patients with differences in the vertical deviation between near and distance were reviewed. Most cases were combined with strabismus surosadductorius and strabismus dorsosadductorius. In 15 of the 19 patients the vertical deviation increased and in four patients it decreased at near fixation. We agree that supranuclear or internuclear misinnervation most likely explains the connection between elevation and accommodation and convergence. A more peripheral innervational abnormality can be excluded because there is no elevation of the left eye when the patient is looking to the right (no aberrant innervation between the fibres to the medial rectus and superior rectus).

In our patient it is unclear whether the abnormality was congenital and decompensation of hyperphoria increased symptoms, or whether it was acquired. Increased vertical fusion range argues for a longstanding squint. The history of most patients in the literature was similar, with slow increase of diplopia and vertical deviation at near over several years. In several patients, combined amblyopia or other strabismus forms—such as dissociated vertical deviation—argue for an early onset of the eye motility problem. Interestingly, one patient seemed to have developed the vertical deviation in combination with convergence after trauma. It is possible that the aberrant re-innervation can be either congenital or acquired. It would be interesting to investigate systematically the influence on near and distance fixation in patients with vertical squint.

References

Tetracycline induced green conjunctival pigmentation deposits

There have been no reports, to our knowledge, of a clinical presentation of ocular pigmentation secondary to the use of oral tetracycline alone. Tetracycline hydrochloride is not a well recognised cause of ocular pigmentation changes, but has been reported to cause pigmentation of teeth and nails. Most of the tetracyclines, minocycline (a second generation drug) is most often associated with the adverse effect of pigmentation. There have been several case reports of minocycline induced scleral pigmentation. Ocular pigmentation changes reportedly caused by tetracycline have been noted in association with use of minocycline. Both patients in these case reports had had tetracycline/minocycline therapy for more than 10 years for acne vulgaris and had their deposition localised within the tarsal conjunctiva. It is believed that most of the cysts are found at the inferior border of the lower tarsus because of the frequency of pre-existing invaginations of conjunctival epithelium in

Figure 1 Patient fixating at near with large left over right squint (A) and at distance with no manifest vertical deviation (B). Eye movement recordings of patient during near and distance fixation demonstrating a slow upward drifting of the left eye, which occurred simultaneously with the convergence movement (C).
this location. The question was raised that long term tetracycline has an effect on the lipid layer of the tear film; noting that the pigmentary deposits were only seen in the conjunctival cysts over the tarsal conjunctiva. Recently, there has been a case report of a patient with a 3 year history of minocycline use for rhematoid arthritis who developed focal palpebral conjunctival pigment deposits. This patient did not have a reported use of tetracycline.

Our patient was taking only tetracycline without concomitant or previous minocycline use and had bulbar conjunctival lesions. Our patient had also been on tetracycline for 2½ years.

Case report
A 48 year old healthy white asymptomatic man presented for evaluation of “green crystals” on the conjunctiva of both eyes (fig 1). The patient had noted the onset of this pigmentation over the previous several months. The patient was treated for acne vulgaris with tetracycline 500 mg a day for the past 2½ years. He denied the use of any topical ophthalmic drops. He took Lotensin for the treatment of hypertension. Past medical history was otherwise unremarkable.

On examination the patient was noted to have several dark green granular deposits on the temporal bulbar conjunctiva of both eyes. The granules appeared discrete, crystalline, and varied in size. Otherwise, the examination was unremarkable. Pigmentation was not noted in any other region.

Pathology
Pathology confirmed the presence of tetracycline. The specimen was positive for a non-polarisable foreign material in a submucosal and intraepithelial distribution (fig 2). This material was calcified and had a faint brown-yellow tinge. There was no appreciable inflammatory reaction or giant cell reaction to the material. Pathology was consistent with that of previously described reports of tetracycline.

Comment
Tetracyclines of the first generation (tetracycline, oxytetracycline, and tetracycline chloride) are the most commonly prescribed oral antibiotics for acne. Tetracycline has also been shown to result in improvement of the ocular manifestations of rosacea. Both conditions are frequent; thus, the ophthalmologist will encounter many patients being treated with tetracycline. Tetracycline fluorescence has been detected in the conjunctiva of all patients who have taken tetracycline orally. Fluorescence was not generalised but was restricted to a thin film-like layer on the surface and to small areas in the surface layer of cells.

This is the first case report, to our knowledge, of clinically visible conjunctival bulbar deposits caused by the use of tetracycline without a history of minocycline use. Pigmentary changes may initially be noted by the ophthalmologist, as in our case report.

It is important to recognise signs of tetracycline pigmentation as it is a commonly used medication, and cessation of the medication may help avoid further pigmentary changes.

References
underlying dry eye state. If tear deficiency and degree of astigmatism are extreme, de-escation of the corneal epithelium is possible, leading to non-healing defects and associated sequelae.

In cases where high or irregular astigmatism is associated with postoperative non-healing corneal defects, addressing the degree of corneal astigmatism may help restore physiological tear dynamics and resolu-
tion of the epithelial defect. Corneal sutures may themselves impede epithelial migration,1 but if this were the only explanation all grafts would be exposed to the same risk. Conversely, not all patients with high astigmatism (non-surgical) have epithelial defects. This would suggest that more than a single factor is at play in such situations. To our knowledge high astigmatism as a contributory factor to development of persistent epithelial defects post operatively, has not been previously considered.

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Reference

Non-tuberculous mycobacteria related infectious crystalline keratopathy

Non-tuberculous mycobacteria (NTM) or atypical mycobacterial keratitis is an uncommon condition causing indolent corneal ulceration. The infection mimics herpetic, mycotic, and Nocardia keratitis and diagnosis requires a high index of suspicion. We report two cases of NTM infection where the presenting sign was that of crystalline kera-
topathy. Both cases were diagnosed by microbial culture and successfully treated.

Case 1
A 44 year old white female contact lens wearer presented with a 3 week history of an inflamed eye with a 1.5 mm diameter area of corneal stromal infiltration. Vision was 6/6 in each eye. She was being treated with antivirals and later unsuccessfully with anti-
bacterials and steroids. Three active stromal crystalline infiltrates appeared in the mid-
stroma 3 weeks later (fig 1). Culture from a corneal biopsy revealed Mycobacterium chelonei.

The keratitis responded to topical amikacin and amphotericin B, which was started on the suspicion of fungal keratitis, before microbial culture results were available. The keratitis resolved over a 4 week period and vision settled at 6/9.

Case 2
An 80 year old white woman with pseudo-
phakic bullous keratopathy had a penetrating keratoplasty and was given systemic tacrolimus. Three months postoperatively she pre-
sented with endothelial dusting and a 1 mm mid-stromal abscess with a crystalline appearance (fig 2). A corneal scrape revealed acid fast bacilli for which she was com-
menced on topical ciprofloxacin and amika-
cin 2.5% but was slow to respond. Culture confirmed Mycobacterium chelonei resistant to amikacin. Topical moxifloxacin was added and oral clarithromycin commenced. Three months later, the ulcer healed with a clear graft but the vision did not improve (counting fingers) on account of pre-existing macular oedema.

Comment
Non-tuberculous mycobacteria cause indol-
ent corneal ulceration resembling herpes virus, fungal, or Nocardia keratitis. The vari-
able clinical presentations and poor suscepti-
ibility to conventional antibacterials usually results in a delay in diagnosis.1** The two common types of NTM causing keratitis are

M chelonei and M fortuitum. The clinical features of NTM include pseudodendritic epithelial defects, subepithelial white fluffy infiltrates with crystalline satellite lesions and ulcers with an overhanging necrotic edge and a grey sloughed base.1 Kerat precipi-
tates and endothelial deposits may appear. Early diagnosis is difficult and absence of organisms in smears and cultures does not exclude the diagnosis of NTM. Repeat scrapes or a corneal biopsy should be considered in all indolent corneal ulcers. Amikacin has been the drug of choice in Nocardia and atypical mycobacterial infec-
tion. However, approximately 60% of patients will not respond to topical amikacin, as with our second case, and use of combina-
tion therapy with ciprofloxacin, gatifloxacin, moxifloxacin, and clarithromycin is recom-

end.4 Penetrating keratoplasty is per-
formed when stromal infiltration is extensive5 but immunosuppression may pre-
dispose to recurrent infection. Both our patients were treated successfully. The first patient had a good visual outcome but the second had poor vision due to pre-existing pathology. Successful treatment requires dis-
 ease awareness, deferring the use of steroids when no organism has been isolated and use of effective antibiotics.

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References

Figure 1 Case 1 showing three active stromal crystalline infiltrates central to the edge of the ulcer.

Figure 2 Case 2 showing a mid-stromal abscess with a crystalline appearance at 5 o’clock region of the graft-host junction.
Xanthogranulomatous disease in the lacrimal gland

We report three cases of adult lacrimal gland xanthogranulomatous disease that demonstrate the spectrum of this disorder and provide insight into immune dysfunction.

Case 1
A 23 year old asthmatic female had 1 year of bilateral, painless, lacrimal gland masses from polyclonal B cell (CD 20+) infiltration (fig 1A, B). The patient was asymptomatic for 18 months after external beam radiation (25 Gy in 10 fractions). While 7 months pregnant, painless lacrimal gland enlargement recurred, as firm, yellow, nodular masses (fig 1C). A second biopsy showed foamy histiocytes, Touton giant cells, and lymphoid infiltrate without necrobiosis (fig 1D). The orbital masses have remained stable 2 years after corticosteroids and surgical debulking. Systemic involvement included breast MALT type lymphoma 4 years after presentation.

Case 2
A 49 year old Brunei male had 10 years of bilateral, yellow, mildly steroid responsive, superolateral orbital masses (fig 2A). Previous biopsy showed benign, polyclonal lymphocytic proliferation in the lacrimal gland and eyelid xanthoma. Second eyelid and lacrimal gland biopsy demonstrated xanthogranulomatous infiltrate involving orbitalis and lacrleys with some germinal centres, s100 negative, KPI positive foamy histiocytes and Touton giant cells, respectively (fig 2B-D). Orbital findings improved with Solumedrol (3 g over 3 days), ciclesporin, and cyclophosphamide. The patient was lost to follow up after 6 months.

Case 3
A 52 year old white female had 2 months of bilateral, yellow, lacrimal gland masses and dry eye (confirmed by Schirmer’s testing) (see fig 3A–C). Lacrimal gland biopsy demonstrated foamy histiocytes, Touton giant cells, chronic inflammation, bands of fibrosis, and necrobiosis. The lacrimal gland masses resolved at 2 years after treatment with Solumedrol (3 g over 3 days), methotrexate, pulsed cyclophosphamide, and topical 0.05% ciclesporin (Restasis) (fig 3E–F). She is maintained on prednisone 40 mg per day, methotrexate 17.5 mg per week, and Restasis twice a day. Systemic associations included asthma, cervical, axillary, hilar lymphadenopathy, iliac, sacral, L4 sclerosis, and xanthogranulomatous disease of the breast for which she underwent mastectomy 3 months before presentation (fig 3D).

Figure 1 (A) T1 weighted axial magnetic resonance imaging (MRI) showing bilateral lacrimal gland enlargement. (B) Initial lacrimal gland biopsy showing a dense lymphocytic infiltrate with preserved ducts (haematoxylin and eosin stain, original magnification 4x). (C) Clinical photograph of yellow, recurrent mass, right orbit, 2 years after radiation treatment. (D) Second lacrimal gland biopsy showing Touton giant cells, foamy histiocytes, lymphocytes, and plasma cells (haematoxylin and eosin stain, original magnification 60x). (E) Clinical photograph of patient showing improvement 1 year after treatment.

Comment
Adult xanthogranulomatous disease is a class II histiocytic disorder syndromically classified as adult onset xanthogranuloma (AOX), adult onset asthma and pericocular xanthogranuloma (AAPOX),1 necrobiotic xanthogranuloma (NBX),3 and Erdheim-Chester disease (ECD).4 AOX has B cell mediated findings including foamy histiocytes and Touton giant cells (fig 2B-D). Orbital findings improved with Solumedrol (3 g over 3 days), ciclosporin, and cyclophosphamide. The patient was lost to follow up after 6 months.

All our cases had asthma. Case 2 had elevated serum protein. Case 3 had lymphadenopathy, salivary gland enlargement, and bony sclerosis. Cases 1 and 3 had breast masses: MALT type lymphoma postdated orbital disease in case 1; xanthogranulomatous disease preceded orbital involvement in case 3. The first two cases could be classified as AAPOX. Case 3 had necrobiosis suggesting NBX, but had clinical features of AAPOX and lacked skin ulcers. These findings demonstrate the adult xanthogranulomatous syndromes are not mutually exclusive.

Xanthogranuloma histology consists of non-Langerhans, lipid laden histiocytes, Touton giant cells, and varying degrees of lymphocytic infiltrate, fibrosis, and necrosis (necrobiosis). This infiltration replaced the normal lacrimal gland architecture causing mass effect and loss of tear production. This same process affected the breast in case 3.

The immune cascade leading to this histopathological appearance is unknown. Our previous work found a predominance of CD8 (cytotoxic) T cells in areas of fibrosis and lipophage accumulation. We postulated that CD8 cells activated histiocytes and fibroblasts. Relevant to this hypothesis, it is fascinating that polyclonal B cell (CD20+) infiltration, without gland destruction or foamy histiocytes, preceded the development of xanthogranuloma in cases 1 and 2 and in one case from the literature6 (fig 1B). An additional report was initially diagnosed as Sjögren’s syndrome, but lacked histology.9

Moreover, case 1 developed a monoclonal proliferation of B cells in the breast 1 year after the orbital xanthogranuloma.

Our cases are unusual because the orbital xanthogranuloma were limited to the lacrimal gland, which is devoid of fat. We found four similar reports (table 1). Perhaps immune dysregulation leads to tissue destruction, and the resultant cell membrane fatty acids are scavenged by malfunctioning histiocytes.

The best treatment for xanthogranulomatous disease is unknown. Our patients had some response to steroids, with cases 2 and 3 responding to B cell (cyclophosphamide and methotrexate) and T cell (cyclosporin) suppressors.

These cases raise questions regarding the pathogenesis of non-Langerhans histiocytosis and demonstrate that histopathological and clinical findings must be used for diagnosis in the spectrum of disorders that is xanthogranulomatous disease.

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<th>Reference</th>
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| Other cases report dry eye, or lacrimal gland involvement, but not specifically presentation in the lacrimal gland. |

References
Management of phaeniciatic ophthalmomyiasis externa

Ophthalmomyiasis, maggot or fly larvae infestation of the eye, is a rare condition that can have variable presentation depending on the type of fly, the ocular structures involved, and the level of larval infiltration.

Case report

A 60 year old African-American male presented with a chief complaint of a swollen, moderately painful red right eye since 4 am that day. Ocular history was significant for foreign body lid trauma of unknown etiology (presumably a rock or insect) 2 days earlier while riding his motorcycle without protective goggles.

Ocular examination revealed 20/20 vision in each eye with correction. Pupils, extraocular motilities, and confrontation fields were normal. Slit lamp evaluation revealed upper and lower lid oedema with mild erythema in the right eye. A 1.5 mm round ulcerated lesion was noted on the right outer canthal region that appeared to pulsate as the patient was examined in the slit lamp (fig 1). The left eye and other ocular structures in the right eye were unremarkable.

Upon external digital pressure of the ulcerated lesion, a foreign organism was seen to retreat into the ocular tissue. Manual forceps were used to remove a 1.0 cm long white segmented maggot (fig 2). This specimen was identified by an entomologist under a microscope, as being of the Calliphoridae family, Phaenicia lucilia, otherwise known as a screwworm fly.

The patient was given erythromycin ointment for use twice a day over the lesion. After 3 days, the patient returned with complete resolution of the lid oedema and erythema (fig 3).

Comment

Ophthalmomyiasis is generally caused by sheep botflies and flesh flies. The most commonly reported organism in the literature is Oestrus ovis, a botfly highly prevalent in sheep herding and farming communities. These flies typically lay their eggs on decaying organic material, but are also attracted to open mucopurulent human sores. Within 24 hours, these eggs hatch, producing larvae which then feed on human tissue. This case was somewhat unusual in that trauma was the mechanism by which the fly eggs were...
Vitreous haemorrhage associated with *Gingko biloba* use in a patient with age related macular disease

*Gingko biloba* extract is a widely used herbal extract that is readily available as an “over the counter” product. It is most commonly used for improving mental alertness and memory. One of its components, ginkgolide B is a potent inhibitor of platelet activating factor. Long term use has been associated with increased bleeding time and it can potentiate the anticoagulant effects of aspirin and warfarin.

This is a case in which the regular use of *Gingko biloba* was associated with a vitreous haemorrhage in a woman with a subretinal neovascular membrane, who had no other risk factors for haemorrhage.

A 78 year old woman, who was otherwise fit and well, first presented in July 2001 to the ophthalmology department in Cheltenham General Hospital with a history of floaters in both eyes. Her visual acuities were 6/6 in the right eye and 6/12 correcting to 6/9 in the left eye. Fluorescein angiography confirmed exudative age related macular disease (ARMD) on the left but no treatable discrete neovascular membrane. She had further loss of vision in the left eye and by October 2002 her left eye vision had deteriorated to 3/60. She experienced a gradual deterioration of vision in the right eye until February 2004, when she presented with rapid visual loss in the right eye to 6/24. An untreatable occult choroidal neovascular membrane was demonstrated on fluorescein angiography. In June 2004 she noted a further sudden drop in central vision in the left eye. On examination she had extensive preretinal and subretinal haemorrhage. Within the next month she developed a dense vitreous haemorrhage reducing her visual acuity to hand movements. A B-scan ultrasound confirmed the vitreous haemorrhage and showed a flat retina with a haemorrhagic elevation at the posterior pole consistent with exudative age related macular disease (fig 1). On further questioning she revealed that she had been taking *Gingko biloba* for the past 5 months. She was also taking vitamin C 1 g daily, zinc, lutein, B complex, fish oil, Fosamax, and a steroid inhaler for asthma. She was advised to stop this combination of medicines when being asked about their drug interactions and, as a result, we are largely unaware from scientific scrutiny and product regulation and, as a result, we are largely unaware of their full adverse effects profile and possible drug interactions. It should be made a regular practice to specifically ask patients about the use of any herbal remedies or unconventional medicines.

Another case of vitreous haemorrhage associated with the use of *Gingko biloba* has been reported in a patient with no other risk factors for haemorrhage. A 59 year old man underwent liver transplantation for cirrhosis caused by hepatitis B infection. This was complicated postoperatively by a large subdural haematoma. Three weeks later he developed a right vitreous haemorrhage.

There are several reports in the literature linking the use of *Gingko biloba* with spontaneous haemorrhage. These include the report of a subdural haematoma, hyphaema, sub-arachnoid haemorrhage, and intracerebral haemorrhage.

**Comment**

A study evaluating the causes of 653 cases of spontaneous vitreous haemorrhage found ARMD to be a small yet significant cause. A study by el Baba et al showed that in 19% of reported cases of ARMD complicated by massive intraocular haemorrhage, the patients were taking warfarin or aspirin.

Vitreous haemorrhage is found to have a significantly higher incidence in patients taking warfarin or aspirin when the bleeding occurred.

This case supplements a series of case reports implicating the use of *Gingko biloba* in spontaneous haemorrhage. There is a danger in the widely held belief that herbal remedies are benign. Patients often omit to tell their doctors of these supplemental medicines when being asked about their drug history. Herbal remedies have been exempt from scientific scrutiny and product regulation and, as a result, we are largely unaware of their full adverse effects profile and possible drug interactions. It should be made a regular practice to specifically ask patients about the use of any herbal remedies or unconventional medicines.

**References**


**Figure 1** Colour fundus photograph of left eye showing extensive macular scar.

**Figure 2** B-scan showing vitreous haemorrhage and haemorrhagic elevation at posterior pole.

**Figure 3** Complete resolution of the lid oedema and erythema.
The legal requirement for driving in the United Kingdom is met following pupil dilatation

Dilatation of the pupil (mydriasis) is a component of a comprehensive ophthalmic examination and is becoming part of the eye examination routine for optometrists in the United Kingdom. As many patients drive to attend their examinations, concerns have been raised regarding the effects of pupil dilatation on driving and whether or not the standard visual performance, specifically on the detection and recognition of low contrast road obstacles and the ability to navigate around them. These findings, together with our results, suggest that satisfying the UK visual standard for driving does not preclude a decrease in driving performance. Therefore, all patients should be advised that although the visual standard for driving may be met following mydriasis, caution is advised when driving after pupillary dilatation.

Report

Twenty adult subjects (mean age 24 years) with normal or corrected to normal visual acuity participated in the study. A selection of six different pairs of number plates (black on white and black on yellow), which conformed to the current UK visual standard for driving (that is, after 1 September 2001), was constructed for the study. Monocular and binocular distance logMAR visual acuity and binocular number plate readings were made before and after mydriasis (of at least 6 mm diameter) with 0.5% tropicamide. Each subject performed the number plate test under standard Driving Standards Agency conditions (outside) at a fixed test distance of 20 metres. A pass at the number plate test required all numbers and letters to be read correctly. Letter by letter scoring was used to record visual acuity. Data were analysed using paired t tests (one tailed) as appropriate. Subjects were also asked for their views on the effects of mydriasis using a questionnaire. The study therefore met the tenets of the Declaration of Helsinki and approval of the protocol was obtained from the institutional human research ethics committee.

All subjects met the legal requirement for driving both before and after dilatation, irrespective of the number plate used. Visual acuity decreased (average of three letters worse) following dilatation (p<0.05 for right eye, left eye and binocular visual acuity results) (table 1) .

Following mydriasis, 13 subjects reported an increase in glare, 15 felt more sensitive to light, 14 reported blurry distance vision, five reported blurry near vision, and one subject reported no effect of the drops. Most subjects reported a slight (nine) or moderate (10) effect of the drops; however, the majority (19) felt confident enough to safely drive home after dilatation.

Comment

Despite a loss in visual acuity after dilatation, all subjects passed the number plate test both before and after dilatation and irrespective of the background colour of the number plate. Recently, Goel et al found a significant number of patients (four of 28) did not pass the number plate test after mydriasis. However, subjects in our study were relatively young, wore the appropriate refraction and were free from signs of ocular disease. Given the small effect of mydriasis on visual acuity, it is not surprising that, for our subjects, mydriasis did not affect the UK visual standard for driving. Notwithstanding the relatively small loss in visual acuity, most subjects in our study reported a slight or moderate effect of mydriasis on their vision. Nevertheless, all subjects but one felt confident enough to drive home.

Wood et al have shown that mydriasis has a measurable decrease on real life driving performance, specifically on the detection and recognition of low contrast road obstacles and the ability to navigate around them. Combined with our results, these findings, together with our results, suggest that satisfying the UK visual standard for driving does not preclude a decrease in driving performance. Therefore, all patients should be advised that although the visual standard for driving may be met following mydriasis, caution is advised when driving after pupillary dilatation.

Table 1

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Hydrated scleral buckle: a late complication of MAI explants

Several long-term complications have been reported with MAI scleral buckles, one a synthetic hydrophilic scleral buckling element, first introduced in the 1970s. We present a case of an extruding, hydrated MAI scleral buckle that presented as an orbital lesion. The magnetic resonance imaging (MRI) characteristics of the hydrated MAI buckle are also described.

Case report

An 81-year-old woman was referred to the orbital service for evaluation of a freely mobile, non-painful conjunctival inclusion cyst presented in the left eye present for at least a year. The extracocular movement was full but with a small left exotropia in primary gaze. Anterior segment examination revealed a firm, nodular subconjunctival lesion in the superomedial quadrant. The diagnosis of extruding scleral buckle versus a large orbital conjunctival inclusion cyst was entertained. She, however, denied a history of retinal detachment repair.

The patient underwent MRI of the orbits with and without gadolinium infusion which revealed a 2.5 × 0.7 cm^2 elongated, elliptical mass in the medial intracranial space. The hyperintensity of the mass on T2 weighted images, indicative of high water content, led to the mistaken radiological diagnosis of a cystic, fluid filled lesion (fig 1). Intraoperatively, a swollen intact segmental buckle was encountered that disintegrated into small and large pieces when grasped with a forceps. Complete meticulous removal of these small fragments was performed (fig 2).

Comment


Figure 2 Hydrated, friable buckle removed in multiple small fragments.

buckle with erosion and extrusion of the explant. Owing to their hydrophilic nature, buckles tend to swell, become bulky, and displace from their intended position. These explants change from an opaque, soft, spongy, whitish appearance to a translucent, gel-like, cream coloured material with hydration. They become extremely friable and fragment easily with slight traction upon removal. Scanning electron microscopy of these hydrated buckles has revealed distortion of the micropore architecture.

The presentations of hydrated MAI buckles are varied. They can become extremely loose and migrate anteriorly, or enlarge in situ and present as orbital masses. Since complications do not occur until many years after the orbital surgery, the history of a retinal detachment repair may not be elicited. In addition, these loose buckles usually do not indent the globe and may not be recognised as being present on indirect ophthalmoscopy.

Radiological imaging may be helpful. MRI T1 weighted images of a hydrated buckle reveal a well defined, hypointense mass, while T2 weighted images reveal a hyperintense mass as a result of high water content. (In contrast, the silicone element will be black on MRI images.)

Removal of hydrated MAI buckles can be very difficult. Careful sub-Tenon dissection should be carried out since any pressure on the buckle can lead to its fragmentation. The procedure is often complicated because of the extremely friable nature of these buckles. Cryoprobe has been used successfully in some cases for removal of the buckles. Le Routie et al demonstrated that removal of MAI buckles with a cryoprobe is both safe and effective technique with lower fragmentation rate compared to the use of forceps. The cryo-probe allows the water in the swollen explant material to freeze, which helps to reduce fragmentation.

In conclusion, ophthalmologists should be aware of the possible complications of the MAI hydrogel buckles. Knowledge of the MRI characteristics of hydrated MAI buckles may be helpful in identifying them in the event they present as a space occupying orbital mass.

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Figure 1 T2 weighted MRI image reveals a hyperintense mass exhibiting a mass effect on the left globe.

References


Complex I respiratory defect in LHON plus dystonia with no mitochondrial DNA mutation

Leber hereditary optic neuropathy (LHON) sometimes occurs with dystonia in association with mitochondrial DNA (mtDNA) mutations in complex I. We describe a patient with LHON plus dystonia who had a severe complex I respiratory defect with no pathological mtDNA mutation, implying a mitochondrial abnormality of nuclear origin.

Case report

The proband was healthy until age 17 years when she developed progressive right sided weakness followed 3 years later by a left hemiparesis with involuntary posturing of the left arm and leg. Intelligence was average, and she finished grade 6 at school. Her parents were unrelated, and she had five healthy siblings.

Neuro-ophthalmological examination at age 23 documented excellent afferent and efferent visual functioning with no Kaisere-Fleischer ring. Optic discs were hyperaemic and slightly elevated with peripapillary telangiectasia in both eyes (fig IA and B). She had modest right sided dystonic features, diffuse hyper-reflexia greater on the right, bilateral Babinski signs, and dystonic posturing on the right while walking.

On return 21 months later, she reported that the vision of both eyes had declined 9 months previously. Visual acuity was 20/100 in both eyes with poor colour vision in both eyes, a mild left afferent papillary defect, and bilateral optic atrophy with no residual hyperaemia or peripapillary telangiectasias (fig 1C). Gait was somewhat worse, and she was modestly dystarhic. Vision did not improve during 18 months of follow up.

Normal laboratory studies included haemoglobin, liver and renal function, serum lactate, pyruvate, and 24 hour urine copper excretion. Cerebral spinal fluid (CSF) lactate acid was slightly elevated (2.8 mm/l with normal range 0.6–2.2 mm/l), and brain MRI revealed atrophy in both basal ganglia (fig 1D).

After signing informed consent, the proband, her mother and father, and four siblings had blood drawn for DNA extraction, polymerase chain reaction amplification, and sequencing of the entire mitochondrial genomic coding region as previously described. Sequence results were compared to Mitomap (www.mitomap.org/mitomap/mitoseq.html), the human mitochondrial genome database (www.genpat.uue.se/mitDB), GenBank (www.ncbi.nlm.nih.gov/Genbank/index.html), and...
Optic discs, pseudopapilloedema, and peripapillary telangiectasias. She went on to develop bilateral optic nerve injury typical of LHON. She also had progressive basal ganglion and upper motor neuron disease culminating in bilateral spasticity, a broad based and unsteady gait, dystonia, and dysarthria. Her clinical course, elevated CSF lactate, normal urinary copper excretion, and severe complex I respiratory defect imply a mitochondrial mechanism for optic nerve and brain injury.

Mitochondrial complex I dysfunction in the absence of a pathological mtDNA mutation provides presumptive evidence of a mitochondrial abnormality of nuclear origin. Complex I dysfunction has been identified in patients with sporadic focal dystonia, and at least one familial generalised dystonia syndrome had a defined nuclear mutation affecting a mitochondrial protein. Other patients with LHON plus dystonia have had complex I mtDNA mutation(s), so this patient broadens the genetic spectrum in which the phenotype may be expected.

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References

Retinal haemorrhages in a young patient with homocysteinuria

The most common ocular complication in homocysteinuria is lens subluxation. We present a patient with homocysteinuria who developed subhyaloid haemorrhages during pars plana vitrectomy/lensectomy for a subluxated lens in the right eye. She had also developed preretal and intraretal haemorrhages in her fellow eye 6 months earlier,

A normal control group of 119 people with no medical problems, who share similar ethnicity with the proband. Mitochondrial respiratory function in complexes I, III, IV, and V was assessed in the proband and one unaffected sibling using a previously described flow cytometric functional analysis method. The proband, her siblings, and their mother had one mtDNA sequence variant recognised as a polymorphism in the Japanese population, which was not present in the 119 normal controls of similar ethnicity. Thirteen previously reported homoplasmic mtDNA polymorphisms were detected in the proband, her family, and the control group. The proband, but not her unaffected brother, had a severe respiratory defect in complex I (fig IE, F, and G).

Comment
This young woman’s initial examination was significant for normal vision with hyperaemic optic discs, pseudopapilloedema, and peripapillary telangiectasias.
after phacoemulsification of the subluxated lens. No preoperative or intraoperative anti-
ocagulation was used for either eye surgeries.

Case report
A 12 year old girl with homocysteinuria presented with decreased vision in the right eye as a result of an anteriorly luxated lens causing pupillary block glaucoma with an intraocular pressure (IOP) of 50 mm Hg. The posterior segment was normal. She had undergone phacoemulsification and anterior vitrectomy for pupillary block glaucoma caused by subluxated lens in the fellow eye 6 months earlier. Retinal examination post-operatively revealed preretinal and intraretinal haemorrhages in the mid-periphery (fig 1), which cleared spontaneously over the next 5 months.

Since medical therapy was ineffective in the right eye, she underwent pars plana lensectomy and vitrectomy. As the core vitreous was intact, small subhyaloid haemorrhages were noted to develop in the mid-periphery. The vitrectomy settings were changed to a high cutting speed and low aspiration but the haemorrhages continued to form. Induction of the posterior vitreous detachment was aborted when peripapillary intraretinal haemorrhages were noted to develop.

On the first postoperative day, a 2 disc diameter subhyaloid haemorrhage (not seen at the end of the surgery) was noted in the macula (fig 2). All haemorrhages resolved spontaneously over the next 10 weeks.

Comment
The precise mechanism of action of homocysteine on the vascular tree is not well understood. Elevated homocysteine levels can cause endothelial disruption, structural damage by toxic effects on the intima and media, increased oxidation of low density lipoproteins, and alterations of clotting factors leading to a hypercoagulable state.3 Histopathological data derived primarily from animal models demonstrate smooth muscle cell hypertrophy and hyperplasia of the arteries.5 Postmortem studies of hyperhomocysteinaemic patients have shown intimal and medial thickening with disruption of the internal elastic lamina of small and large vessels.4 Histopathology of small arteries reveal focal proliferation of connective tissue with increased fibroblasts, collagen, and irregular elastic fibres. These changes may contribute to the fragility of small arteries and capillaries.

Valsalva retinopathy sometimes occurs with general anaesthesia. We do not believe this patient experienced this mainely because Valsalva retinopathy is bilateral. The retinal haemorrhages occurred only in the operated eye and not the fellow eye each time the patient underwent surgery.

The haemorrhages noted postoperatively in the left eye may have occurred because of ocular decompression retinopathy. An acute lowering of IOP can decrease the resistance of the retinal and choroidal circulation, temporarily overwhelming the capacitance of the capillary bed and resulting in multiple endothelial leaks and intraretinal haemorrhages. Hyperhomocysteinemia can affect the autoregulation of small arteries.6 This may have contributed to the development of retinal haemorrhages in the left eye. The subhyaloid haemorrhages in the right eye, however, were unlikely to be related to ocular decompression retinopathy since no haemorrhages were present post pars plana lensectomy, but these developed soon after vitrectomy was initiated. Minimal traction transmitted to the internal limiting membrane and nerve fibre layer by the vitreectomy may have caused the extremely friable superficial capillaries to rupture. Indeed, defects in retinal vascular autoregulation due to homocysteinuria, may have contributed to the development of the observed haemorrhages.

We hypothesise that individuals with chronic hyperhomocysteinemia are at an increased risk for retinal haemorrhages because of homocysteine mediated destructive changes in small vessel walls and an autoregulatory defect that results in extreme capillary fragility.

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References

Internet based ophthalmology service: impact assessment
In 2003, the Department of Health, Western Australia, commenced a teleophthalmology service between Carnarvon Regional Hospital (CRH) and Lions Eye Institute (LEI) at City of Perth (at 940 km), pioneering the use of remote, interactive consultations in ophthalmology. This assessment (a) reports the impact of teleophthalmology service on patient diagnosis, management, outcomes, and satisfaction; and (b) estimates the costs of teleophthalmology service.

Case report
An internet based system (www.e-icare.com) developed and evaluated at LEI, was used to store and transmit multimedia data to a secure, central database.7 Practitioners at CRH collected these data, which included patients’ demographic details, medical history, and ocular images. A portable slit lamp developed at LEI,8 tonometer (Keler Pulsair 3000, Japan), and digital retinal camera (Canon CR-45NM, Japan) were also used. A questionnaire and interview approach assessed the satisfaction of the patients and practitioners. Estimation of costs analysed additional activity data and associated costs.

During the 12 month study period, there were 118 teleophthalmology consultations (42% men, 58% women, mean age 42 years, range 4–73 years). Most patients (53%) became aware of the service through local media, while health professionals in Carnarvon referred 36% for teleophthal-
mology consultation. Of the 118 cases, 3% of the patients used teleophthalmology for emer-
gency consultation, 94% for testing for glaucoma and diabetic retinopathy; 3% of the cases were for expert second opinion and postoperative follow up.

Teleophthalmology proved to have impact on all the patients, by improving the eye care facility at CRH itself, instead of the need to travel 940 km to the city. Following tele-
consultation, only 3% of patients were referred to a city hospital. While 53% of patients had no abnormalities detected, 3% of patients received treatment at CRH itself. The ophthalmologist recommended regular follow up for 36% of patients seen by tele-
medicine.

PostScript
The teleophthalmology consultation cost per patient, at current efficiency level, is $279.96 including fixed cost. A cost neutral analysis estimated, at optimal efficiency of 352 patients per annum, cost per patient would decrease to $107.72. In the remote area, without teleophthalmology, the cost to the service provider for a face to face consultation with an ophthalmologist was as high as $665.44 per patient. The minimum number of patients needed to make a cost effective teleophthalmology consultation is 126 per annum.

The majority of patients (98%) expressed satisfaction with the internet based consultation and observed it as convenient. Lack of physical contact with ophthalmologist was not a major concern to many patients (74%). CRH practitioners spoke favourably of using teleophthalmology, in that they were able to get advice from colleagues and discuss alternative management strategies. Practitioners at LEI found the experience informative and challenging.

Comment
While acknowledging that face to face consultations with ophthalmologists are unique, its costs are enormous in remote health centres. The project is a technical and clinical success and one that led to direct potential benefits for patients in terms of improved outcomes, as well as considerable educational experience for the participating medical practitioners. However, current assessment brought to light the importance of redefining utilisation criteria in order to achieve efficiency. For example, 126 patients per annum are required for a cost effective teleophthalmology service while the current efficiency rate is 118 per annum (2.2 patients per week). Better coordination between the local healthcare workforce and CRH may increase the number of teleophthalmology consultations, which in turn will help to achieve breakeven or even establish net savings. Overall, this assessment indicates that the success of teleophthalmology will be based upon identifying the requirements of the service and using appropriate technology.

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References

Temperature sensitive oculocutaneous albinism associated with missense changes in the tyrosinase gene
Oculocutaneous albinism (OCA) describes a group of autosomal recessive disorders characterised by reduced or absent pigmentation of the eye, skin, and hair as a result of a congenital reduction in melanin synthesis. Additional findings in the eye include decreased visual acuity, nystagmus, iris translucency, hypopigmentation of the uveal tract and retinal pigment epithelium, foveal hypoplasia, and abnormal decussation of the optic nerve fibres at the optic chiasma leading to a lack of binocular vision.1 Type I OCA results from mutations in the tyrosinase gene and leads to either total absence of tyrosinase activity (OCA Ia) associated with absence of pigmentation (“tyrosinase negative”), or a marked reduction in tyrosine activity (OCA Ib) associated with reduced pigmentation (“tyrosinase positive” or “yellow albinism”). We report a new case of the rare variant temperature sensitive albinism and our identification of missense mutations in the tyrosinase gene, not previously found in this form of albinism.

Case report
The patient, a 31 year old woman, was referred to us for genetic advice. She had originally presented at 6 weeks old with nystagmus and white hair; her parents both have dark hair and olive skin. The diagnosis of oculocutaneous albinism was made at 9 months. As she grew older the hair of her head darkened and, particularly in her teens, the hair on her lower legs and forearms darkened. As an adult she has light blonde hair, darker eye lashes and eyebrows, white axillary and pubic hair, but strongly pigmented hair on forearms and lower legs (fig 1). When examined in the clinic she had reduced visual acuity (6/36 bilaterally), marked iris translucency, and an albinotic retina with foveal hypoplasia bilaterally. Visually evoked potential revealed crossed asymmetry consistent with oculocutaneous albinism. We made a diagnosis of temperature sensitive albinism and searched for mutations in the tyrosinase gene. Blood was taken, with informed consent, from the patient and her parents and DNA extracted using standard techniques. Using polymerase chain reaction we amplified each of her tyrosinase gene exons and sequenced the entire coding region and intron-exon boundaries. Our patient did not have the R422Q mutation previously reported in patients with this phenotype and also did not have two other mutations known to be temperature sensitive.1 We did identify two missense mutations: R217Q and A355P, in exons 1 and 3 respectively (fig 2). The exon 1 mutation had been inherited from her

Figure 1 Clinical photographs of patient. Note the yellow blonde hair, dark eyebrows, and strongly pigmented forearm hair. (Photograph reproduced with permission of the patient.)
Choroidal neovascularisation associated with meningioma

This report documents the occurrence in three patients of subretinal choroidal neovascular membranes (CNVM) ipsilateral to meningiomas involving the optic nerve. We propose that the association might not be coincidental.

Case 1

A 31 year old woman developed a central scotoma in the left eye that led to the diagnosis of a left sphenoid wing meningioma involving the optic canal. The tumour was resected and her vision returned to normal. At age 56 a generalised seizure led to recognition of a recurrence. When the recurrent tumour was resected it proved to be a malignant meningioma. She was then treated with photon radiation from a 10 MV linear accelerator using a three field technique (right lateral, left lateral, and superior). The total dose was 45 Gy administered in 25 fractions. Thereafter, on regular follow up eye examinations she had normal visual function, pupils, and fundi. At the age of 64 she had a single episode in which for several seconds she lost all vision in the left eye except for a nasal island. There were no residua but her ophthalmologist found a new fundus abnormality that prompted referral.

Her medical history included migraine and a cutaneous malignant melanoma. There was no pertinent family history.

The patient’s visual acuities were 20/15 in each eye. Her colour vision (Tschirandt) and pupils were normal. The Goldmann visual field of her right eye was full but she had a relative inferior altitudinal defect to the 12e white stimulus in the left eye. There was 3 mm of proptosis of the left eye with normal orbital resiliency. Fundus examination of the left eye revealed a peripapillary supertemporal retinal elevation associated with lipid choroidal neovascularisation (CNVM) (fig 1, top left). There were no macular drusen. Echography showed a 1.1 mm of elevated retina adjacent to the left disc with normal acoustics. The rest of her neuro-ophthalmological examination was normal. There was hyperfluorescence in the area of elevation with late leakage of dye on fluorescein angiography consistent with a peripapillary CNVM (fig 1). At that time magnetic resonance imaging (MRI) scans showed no evidence of recurrent meningioma.

Five years later the vision declined to 20/30 in the left eye. There was neither optic atrophy nor optic disc swelling, but a left afferent papillary defect and dyschromatopsia were observed. MRI showed that the sphenoid meningioma had recurred and involved the intracanalicular and posterior orbital segments of the left optic nerve. There also was enlargement of the posterior bellies of the left inferior and lateral rectus muscles.

References


Figure 2 Mutations in tyrosinase gene.

Chloroquine and breast carcinoma: a case report of a patient with systemic lupus erythematosus

Chloroquine significantly increased the risk of breast carcinoma.

Our patient was heterozygous for missense mutations in the tyrosinase gene that have been previously associated with a temperature sensitive phenotype. We are not aware of other patients with this particular combination of mutations. It has been shown that co-expression of wild type tyrosinase can correct the mutant conformation in temperature sensitive alleles such that exit from the endoplasmic reticulum and degradation by proteasomes and no pigment is produced. At lower temperatures (31°C) the enzyme can be successfully translocated into the melanosomes. Thus, at 37°C mutant R422Q tyrosinase is retained in the endoplasmic reticulum and degraded by proteasomes and no pigmentation will be noted. This observation is based on the phenotype will not be noted. The mutational analysis reveals its temperature sensitive nature indicating that exit from the endoplasmic reticulum and degradation of mutant tyrosinases results in a lack of pigmentation. Thus, at 37°C mutant R422Q tyrosinase is retained in the endoplasmic reticulum and degraded by proteasomes and no pigmentation will be noted.

We propose that the association might not be coincidental.

Case 1

A 31 year old woman developed a central scotoma in the left eye that led to the diagnosis of a left sphenoid wing meningioma involving the optic canal. The tumour was resected and her vision returned to normal. At age 56 a generalised seizure led to recognition of a recurrence. When the recurrent tumour was resected it proved to be a malignant meningioma. She was then treated with photon radiation from a 10 MV linear accelerator using a three field technique (right lateral, left lateral, and superior). The total dose was 45 Gy administered in 25 fractions. Thereafter, on regular follow up eye examinations she had normal visual function, pupils, and fundi. At the age of 64 she had a single episode in which for several seconds she lost all vision in the left eye except for a nasal island. There were no residua but her ophthalmologist found a new fundus abnormality that prompted referral.

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References


Figure 2 Mutations in tyrosinase gene.
2001 she noted blurring of the vision in her left eye and a peripapillary CNVM was discovered. Despite two laser applications the patient’s vision continued to worsen.

Her medical history included rheumatic heart disease, hypertension, and hypercholesterolemia. In February 2001 she had endocarditis complicated by a left hemiplegia. There was no family history of any pertinent disorder.

Her visual acuities were 20/20 in the right eye and 7/200 in the left. She had dyschromatopsia of the left eye with 2 mm of protosis and a relative afferent pupil defect. Goldmann perimetry revealed a full visual field in the right eye and only a residual nasal island in the left. The fundus of the right eye was normal without drusen. Her left optic disc was pale and there was nerve fibre layer swelling and haemorrhage adjacent to the nerve. MRI showed a 1.4×1.2×1.2 cm homogeneously enhancing mass along the left planum sphenoidale extending into the left optic canal consistent with a meningioma.

Case 3
A 47 year old woman noticed that she had a painless visual disturbance of her right eye “like looking through a glass of water.” The symptom persisted, and 2 months later she awoke with a blind right eye. An MRI scan was interpreted as normal and her blindness was ascribed to optic neuritis. She was treated with a course of corticosteroids during which she recovered some vision but her vision failed again after the steroids were discontinued and thereafter she was unable to see light.

She had a history of asthma and obesity. Her father had age related macular degeneration.

At the age of 49 she noticed metamorphopsia in the left eye, and a large, elevated, extrafoveal CNVM was found. Echography revealed 1.3 mm of elevation, which was acoustically normal. Vision was then 20/20. The right optic disc was atrophic and the left was normal. There were no macular drusen. She failed to respond to laser photoagulation and proton beam radiation. Vision failed to 3/200 and the left disc became oedematous. MRI scanning showed bilateral optic nerve sheath enlargement and gadolinium enhancement of the mid and posterior segments of both optic nerves and extension of the lesion on the right side over the planum towards the chiasm. The lesions were interpreted as primary optic nerve sheath meningiomas.

Comment
Choroidal neovascularisation has been associated with macular degeneration, histoplasmosis, pathological myopia, angioid streaks, optic nerve drusen, optic nerve pits, pseudotumour cerebri, chronic inflammation, infection, malignant melanoma, choroidal osteoma, choroidal naevi, photoacoagulation, and choroidal rupture. A break in Bruch’s membrane seems to be a common feature in CNV, but the exact pathogenesis remains a subject of debate.

While we cannot eliminate the possibility that the association of CNV with meningiomas and CNV in our patients is merely by chance, several observations suggest otherwise. In each case the fundus of the fellow eye was free of drusen, let alone more substantive evidence of macular degeneration. None of the patients had a disorder known to predispose to CNV. There has been one report of CNV after radiation but in that case the patient also had significant radiation retinopathy. Our irradiated patient (case 1) had no evidence of radiation retinopathy and the radiation portals spared the eye. One of our patients was only 49 years old when the membrane was recognised. In two of our patients the membrane was peripapillary.

Schatz et al published the histopathological findings in a patient with a primary optic nerve sheath meningioma in which there was a CNV. However, their patient had chronic disc oedema and venous collaterals and had antecedent age related macular degeneration in both eyes. Shields et al described an instance of CNV in a child with an optic nerve glioma. That patient’s disc was also oedematous. Peripapillary CNV has been described with chronic disc oedema of other causes as well, but two of our patients never had disc swelling and the third developed disc oedema only after the CNV was recognised.

How might a meningioma cause an ipsilateral CNV? The pathophysiological mechanism by which these two conditions occur together is unclear. It is possible that the tumour tissue could have invaded the eye. CNV has been associated with other tumours involving the choroid.4 Ocular invasion was not evident on ultrasound (cases 1 and 3) or MRI scans but absence of proof is not proof of absence. In the case of Schatz et al there were small foci of the meningioma in the peripapillary sclera and retro-laminar optic nerve, which were not seen before enucleation.5 Dutton reviewed meningiomas involving the optic nerve and primary optic nerve sheath meningiomas. CNV was not mentioned as a presenting sign. None the less, he calculated 3.7% of 477 reported cases described intraocular invasion by meningiomas.6 Other authors have reported histopathological cases of meningioma invading the optic nerve and disc.12,7

We believe that the association of CNV with ipsilateral meningiomas in our patients was not one of chance. The presumed mechanism is invasion of the globe by the tumour sufficient to cause the CNV but below threshold for detection by MRI, ultrasound, or ophthalmoscopy.

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Intraoperative visual experiences of cataract patients can be both pleasant and unpleasant

We read with interest Zia et al’s article, which highlights a professional artist’s and a poet’s respective renditions of their visual experiences during cataract surgery. While it is unclear from the report whether the artist’s elaborate drawing resembling a “colourful monkey” was associated with a pleasant or frightening visual experience, it appears from the poem that the poet’s visual experience was most probably pleasant and delightful.

We have previously reported that the visual experience during cataract surgery under local anaesthesia can be frightening in up to 16.2% of patients. The anxiety that may result from the intraoperative visual experience is clinically significant because it may cause patients to become uncooperative during the procedure and trigger a sympathetic stress response. This may result in hypertension, tachycardia, ischaemic strain on the heart, hyperventilation, and acute panic attacks. These stress responses are particularly distressing to patients who are often elderly, with systemic co-morbidities such as hypertension and ischaemic heart disease. The frightening experience may also lower patients’ satisfaction with the surgery. The poet’s experience reported by Zia et al reminds us that the intraoperative visual experience during cataract surgery can be pleasant for some patients. In fact, our experience has shown that the majority of patients find their visual experiences pleasant and, in some cases, the visual experience actually increases their satisfaction with the surgery. In a recently reported randomised controlled trial conducted in India involving 304 patients who underwent phacoemulsification under either topical anaesthesia (TA) or retrobulbar anaesthesia (RA), the visual experience was reported by 106 out of 154 (68.8%) TA and 102 out of 150 (68%) RA patients to be pleasant and by 47 (30.3%) TA and 46 (30.7%) RA patients to be unpleasant. In a separate unpublished study conducted in Singapore, eight of 98 patients (8.2%) who had phacoemulsification under TA reported that their satisfaction with the surgery increased because of their visual experiences, whereas only two patients (2.0%) experienced a decrease in satisfaction. The remaining 88 patients (89.8%) reported that their visual experience did not affect their satisfaction with the surgery. Some of the patients who reported their visual experiences pleasant commented on the “fantastic colours” that they experienced. In another similar study on patients who had cataract surgery under RA, nine of 152 patients (5.9%) experienced an increase in satisfaction, whereas five patients (3.3%) thought that their satisfaction had decreased as a result of the visual experiences and the remaining 138 patients (90.8%) experienced no change in their satisfaction.

An additional observation is from video-taped interviews conducted by one of us (CMK) with several leading ophthalmologic anesthesiologists in the United States who had cataract surgery under local anaesthesia themselves. The video recordings were made during the annual scientific meeting of the Ophthalmic Anaesthesia Society held in Chicago in October 2004. The videos clearly showed they all had interesting, pleasant and beautiful images during their surgery.

In summary, patients may experience pleasant or unpleasant visual sensations during cataract surgery under local anaesthesia. Further investigation is warranted to help ascertain how we can reduce the possibility of the experience being unpleasant or frightening.

References


Cigarette pack warning: it can send you blind!

The growing research implicating smoking in age related macular degeneration (AMD) prompted us to write an editorial in 1999 urging the Australian government to warn smokers of this little appreciated risk. In 2000, the Australian National Quit campaign ran an advertisement as part of a series titled “Every cigarette is doing you damage,” which explicitly addressed AMD. A website describes the campaign here in Australia (www.quitnow.info.au/smokescreen/html) and the television ad may be downloaded (www.quitnow.info.au/smokescreen/smokescreen.html).

In 2006 the Australian government will require new mandatory pictorial pack warnings, one of which will be about AMD. This warning was one of the strongest tested among smokers in the research conducted for the government before the announcement. The full report and other related information can be found at tobacco.health.
BOOK REVIEWS

Immunology of the lacrimal gland, tear film and ocular surface

A short quotation (p 152) summarises the book: “These systems are all part of the multiple and redundant and protective mechanisms...[that] maintain a functioning cornea.” Reflecting this complexity, chapters range from the pathogenesis of herpetic keratitis to dry eyes, to mucosal immunity and the use of topical ciclosporin, to tear film and contact lenses and, of course, inflammation. The book includes more unusual chapters on ocular surface: these integrate the eye into the upper aerodigestive tract. Parallels between lacrimal and salivary glands, which are not often conducted, focus attention to the inflammatory and immune processes common to these mucosae and the diagnostic markers they might offer.

Some chapters are dense and scholarly: “Sex, sex steroids and dry eye syndromes” has no fewer than 232 references, and provides a “must read” synthesis of approaches, results and hypotheses of the research undertaken to understand sex related differences in lacrimal and meibomian gland (dys)function. Other chapters have a narrower focus: events leading to Acanthamoeba infections and candidates for therapy are presented in a 26 page bound summary common to these mucosae and the diagnostic markers they might offer.

Equally elegantly and authoritatively presented are hypotheses and results showing that constant parasympathetic input is necessary for tear production and thus ocular surface homeostasis. Though not stated by the editors, this book contains contributions to a meeting with the same title, which provided a wonderful opportunity for discussions. It is rather a pity that these are not part of the book. Putting up with different styles is a small price to pay for this highly informed and expertly abstracted state of knowledge publication.

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Glaucoma. 3rd ed.

This excellent text has been in print since 1989 and its longevity is testament to its high quality. This is the third edition, with a new co-author John Salmon. Since its previous edition over 8 years ago there have been many advances in both the genetics, and the diagnosis, monitoring and treatment of glaucoma. This text successfully updates the previous edition, and provides a concise, systematic, detailed and well balanced representation of modern glaucoma diagnosis and management.

This book is aimed at the trainee ophthalmologist and optometrist, although it is also good basic reading for the practising ophthalmologist. This is a comprehensive text in that each type of glaucoma is described in terms of its main clinical features and management. There are many colour illustrations and photographs, these help the reader to correctly interpret clinical signs and diagnostic tests. It also covers current controversies and new techniques such as non-penetrating glaucoma surgery. The landmark glaucoma studies and their significance are also mentioned. It is perhaps too brief in sections, particularly in the chapters looking at glaucoma diagnosis, perimeter, and imaging; however, adequate and key references are provided to allow further pursuit of these topics in more depth.

The book begins by covering the basic sciences including the physiology of aqueous secretion. Then there is a comprehensive definition and classification of glaucoma. The different types of glaucoma are described at length. Tonometry is covered well, including the range of tonometers, potential errors in tonometry, and calibration. Gonioscopy is discussed including angle structure identification and the different systems of angle classification.

Retinal nerve fibre and optic nerve head assessment is described briefly including the new imaging techniques of scanning laser tomography (Heidelberg retinal tomogram II), ocular coherence tomography (OCT), and scanning laser polarimetry (GDx nerve fibre analyser). The images or readouts produced by each machine are provided in colour along with a very brief description of their interpretation. The various modalities of perimetry are described, their interpretation is given, and new techniques such as the frequency doubling contrast test (FDT) and shortwave automated perimetry (SWAP) are discussed and examples provided.

Glaucoma medications are covered very well. Long standing medication are discussed as well as new treatments options, including combined topical preparations. Neuroprotective agents are covered with the recent research regarding these agents. There is a chapter on laser therapy which covers argon, diode, and selective laser trabeculoplasty, Nd-YAG laser iridotomy, and diode laser cycloablation.

Trabeculectomy surgery with early and late complications are discussed comprehensively. There is an excellent and concise chapter on non-penetrating filtration surgery, covering the two most popular techniques—deep sclerectomy and viscocanalostomy.

The next chapter deals with antimetabolites in filtration surgery; established antimetabolites are covered (5-fluorouracil and mitomycin C), new agents such as antibodies to TGF-β are also mentioned. The final chapter is on drainage implants, the Molteno, Baerveldt, and Ahmed implants are discussed. Finally the actual surgical techniques and the complications are well described.

Overall, this is an excellent book, it is concise, with only 163 pages of illustrated text, easy to read, and extremely pertinent to clinical practice. A text I thoroughly recommend for any trainee ophthalmologist or optometrist and anyone wanting a brief, contemporary revision text on the diagnosis and management of glaucoma. Although, fortunately or unfortunately, in the end it may only whet your appetite for information and leave you wanting more.

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NOTICES

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

Thoughts on Ophthalmology and Development

The Mathis Eye Foundation is a small, privately financed organisation, established 17 years ago by a former international banker who began his medical studies at age 40, with the specific intention of working in third world ophthalmology. The Foundation’s experiences and lessons learned are presented in a 26 page bound summary entitled Thoughts on Poor World Ophthalmology Development, an often critical look at eye surgery programs in Latin America, Africa, and Haiti. To obtain this report without cost, please contact jheatherly@taylormathis.com.

Vision 2020

The latest issue of Community Eye Health (No 94) assesses the progress of Vision 2020 at the district level. 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.Shah@lshtm.ac.uk; online edition: www.jceh.co.uk). Annual subscription (4 issues) £28/US$45. Free to developing country applicants.