Acetazolamide, alternate carbonic anhydrase inhibitors and hypoglycaemic agents: comparing enzymatic with diuresis induced metabolic acidosis following intraocular surgery in diabetes

We describe a case of acetazolamide induced acidosis associated with the precipitation of a hyperosmolar state in a diabetic patient 6 weeks after routine phacoemulsification. While renal tubular acidosis is well reported with acetazolamide, this case suggests that a direct diuresis induced acidosis can also have significant effects, producing serious complications when acetazolamide is prescribed to a diabetic patient, and those with renal impairment, with important implications for prescribing.

Case report

A 47 year old female patient underwent technologically uncomplicated left phacoemulsification with intraocular lens implant in 2002. Medical history included insulin dependent diabetes since 1971. She had treated, stable proliferative diabetic retinopathy, relatively mild diabetic nephropathy (proteinuria with a stable creatinine in the region of 140 μmol/l for several months), and mild diabetic autonomic neuropathy. Serum urea had been slightly raised in the past, though had normalised. Serum electrolytes included normal Na+, K+, and bicarbonate concentrations when acetazolamide was prescribed.

Six weeks after cataract surgery she developed left cysoidal macular oedema. Confirmed by fundus fluorescein angiography, treatment was started with topical ketorolac and frequency of postoperative topical steroid increased. Treatment was later started with acetazolamide 250 mg orally twice a day, with instructions to drink lots of sugar free fluids to compensate for the diuretic effect. Arrangements were made for regular monitoring of her electrolyte status.

The patient started to progressively deteriorate over the next few days, reporting a massive diuresis. She required emergency admission 6 days after starting treatment. Biochemical results are shown in table 1. Subcutaneous insulin was administered and acetazolamide discontinued. A sliding scale of insulin and intravenous saline drip were commenced after admission, when she was recommenced on a subcutaneous insulin regimen and discharged as an inpatient.

**Comment**

This case suggests that the diuretic induced mechanism for acetazolamide acidosis can be a cause of severe metabolic acidosis in susceptible patients, and that the diuresis can be severe enough to precipitate a life threatening diabetic crisis. Carbolic anhydrase inhibitors such as acetazolamide affect the amount of excess body water in a diabetic patient. This makes plausible the postulate that acetazolamide was the culprit. Theoretically, a diabetic ketoacidosis is also possible, though we are unaware of specific reports to date in this context. HONK is arbitrarily defined as serum osmolality >320 mOsm/kg and a glucose blood level >33 mmol/l, without excessive ketones, and

### Table 1: Biochemistry on admission

<table>
<thead>
<tr>
<th></th>
<th>Serum glucose</th>
<th>Serum Na⁺</th>
<th>Serum K⁺</th>
<th>Serum urea</th>
<th>Serum creatinine</th>
<th>Urine ketones*</th>
<th>Serum osmolality†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>55 mmol/l</td>
<td>135 mmol/l</td>
<td>4.0 mmol/l</td>
<td>3.5–5.0 mmol/l</td>
<td>149 mmol/l</td>
<td>0</td>
<td>357 mOsm/kg</td>
</tr>
<tr>
<td>Normal range</td>
<td>3–6 mmol/l</td>
<td>135–145 mmol/l</td>
<td>3.5–5.0 mmol/l</td>
<td>2–8 mmol/l</td>
<td>60–120 mmol/l</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Normally no ketones are detected on stick testing of urine.
†2[Na⁺-K++]+urea+glucose, using serum concentrations; dangerous if outside 240–330 mOsm/kg.

Most reports in the literature do not specify the underlying pathophysiological mechanism causing metabolic acidosis with acetazolamide. Some cases have been suspected to be the result of a biochemical effect operating at an enzymatic level to increase urinary loss of bicarbonate producing a metabolic acidosis— for example, renal tubular acidosis, and potentially also lactic acidosis, damage to the tricarboxylic acid cycle, ketosis and inhibition of pyruvate carboxylase. However, the biochemical results in this patient, together with the rapidity of acidosis, do not suggest a tubular origin for the acidosis. Instead the patient displayed an alternative mechanism that accounts for the metabolic acidosis. This was causing the physiological effect of diuresis causing loss of excess body water in a diabetic patient.

Further, there was no history of biguanide use; metformin is an oral hypoglycaemic agent that can cause lactic acidosis to the extent that it is contraindicated with a creatinine level of 150 μmol/l or more. Basic physiological work suggests that a diuresis induced acidosis can be a significant factor with acetazolamide. Biochemical results in this patient directly correspond to the urine pH and bicarbonate of those obtained when healthy subjects have been given three 250 mg doses of acetazolamide. Acute clinical doses of the drug cause a change in body fluid compartments leading to a moderate isosmotic hypovolaemia with an intracellular volume expansion as well as metabolic acidosis. Three 250 mg doses of acetazolamide in healthy men are associated with a significant 1.7 litres reduction in body water, compartmentalised as a significant reduction in extracellular water and increase in intracellular water. In this patient such a diuresis would have been significant enough when occurring over a few days to produce enough loss of body water to precipitate dehydration and lactic acidosis despite her drinking large volumes of fluids.

Physiological stress of this nature is a well known stimulus that can precipitate a diabetic crisis in a susceptible patient, the massive rise in blood glucose largely accounting for the high osmolality in the patient. Hyperglycaemic hyperosmolar non-ketotic syndrome (HONK) does occur, although less commonly than ketoacidosis in insulin dependent diabetics. This makes plausible the postulate that acetazolamide was the culprit. Theoretically, a diabetic ketoacidosis is also possible, though we are unaware of specific reports to date in this context. HONK is arbitrarily defined as serum osmolality >320 mOsm/kg and a glucose blood level >33 mmol/l, without excessive ketones, and
was clearly induced by the stress of diuresis in this patient, with which it is associated. It would also have compounded the patient’s existing dehydration. Mortality from HONK can be as high as 40% despite hospital admission. It is possible that the precise mechanism of metabolic acidosis seems not to have been considered in most case reports as treatment was, in many ways, unaffected. Alternately, it may be that the effect reported in this case is extremely rare. However, the clinical findings in this case are supported directly by correlation with the findings of basic physiological work on the pharmacodynamics of acetazolamide, together with work on the pathophysiology of HONK. This suggests that the observations made on this case are certainly of much broader significance and raise an issue of concern about the drug’s prescription in both diabetes and renal failure. While manufacturer’s recommendations for acetazolamide in Britain include contraindications to its use in supraphrenal dysfunction, they do not issue cautions for its use in diabetes. Thus this case’s principal value lies in evaluating current prescribing practice, particularly as diabetics are a very common group of patients in ophthalmic practice, and acetazolamide is not uncommonly prescribed in many different areas of clinical ophthalmology, as well as by other clinicians. Until further data are forthcoming, including data on newer slow release formulations, good practice should be to prescribe the drug with especial caution in diabetics, particularly for those conditions, including this case, where its prescription in clinical ophthalmology is methazolamide. The latter is associated with a less profound reduction in intracocular pressure, but also less acidosis.

This case should also serve as a reminder that patients with any level of renal impairment are a group that are vulnerable to acetazolamide toxicity. The data sheet and electronic medicines compendiums state that acetazolamide is contraindicated in marked kidney and liver dysfunction, supraphrenal gland failure, and hyperchloremic acidosis. The British National Formulary is less specific and states that it is contraindicated in renal impairment. We would suggest that diabetic patients with a creatinine level of 140 mmol/l are at quite high risk of nephrotoxic drug reactions, though caution should be exercised in even mild renal impairment.

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Table 2 Arterial blood gases on admission

<table>
<thead>
<tr>
<th>Patient</th>
<th>pH</th>
<th>pCO₂</th>
<th>pO₂</th>
<th>Base deficit [excess]†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal reference range</td>
<td>7.3</td>
<td>3.4 kPa</td>
<td>15 kPa</td>
<td>–10.3 mmol/l</td>
</tr>
<tr>
<td>7.35–7.45*</td>
<td>4.5–6.0 kPa</td>
<td>12–15 kPa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Life threatening at and beyond 7.2 and 7.6.
†Normal >33 mmol/l, <–3 mmol/l = metabolic acidosis, –3 to +3 mmol/l = mild metabolic acidosis, severe metabolic acidosis, or mixed metabolic disturbance.

The art of retinal detachment surgery: a photoessay

Subjective visual experience has been described previously in patients undergoing intraocular surgery, and may occur during either topical anaesthesia or regional anaesthesia (peribulbar, retrobulbar, subtenons). Published reports suggest most or all patients undergoing cataract extraction under local anaesthesia will report some visual symptoms when questioned immediately after their procedures. These symptoms are common therefore and range from perception of light, photopsia, colours, and movement, through to more formed visual sensations such as patterns, instruments, and surgeon’s fingers/hands/detail. It is not surprising that patients undergoing vitreoretinal surgery under local anaesthesia might also experience visual symptoms.

We present illustrations and comments (figs 1–4) made by an artist who underwent retinal detachment surgery. He presented with macula-on retinal detachment successfully repaired by vitrectomy, cryotherapy, and 20% SF6 gas performed by peribulbar anaesthesia. They provide an interesting insight into previously unreported visual experience during vitreoretinal surgery. As visual symptoms are both common, and may be perceived to be frightening in a small percentage of patients, we reinforce the view that informed patient consent procedures should include the possibility of visual experience during vitreoretinal surgery under local anaesthesia.

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References


Figure 2 (A) From time to time liquid was splashed on to the eye, producing quite remarkable starbursts of bubbles and comet trails of light. (B) The brilliant light faded and was replaced by deliquescent magenta coloured shapes, glowing like neon, constantly forming and reforming and with sparks coruscating round the edges … a real fireworks display. (C) Quite suddenly the fireworks gave way to this darker mood … the shapes still forming and reforming but more slowly, no longer glowing, but in a complementary colour to that of the previous image … a muted lime yellow. (D) Next came perhaps the most extraordinary and delightful of all the images … this near perfect facsimile of a Chinese silk painting of bamboos gently swaying, as if in a slight breeze, in front of a full moon. (E) Alas, the “Chinese painting” gave way to the appearance of “long whiskers”—rather like huge stray eyelashes—moving slowly but sometimes jerkily, at the top right of the field of vision. (F) Darker than this, richly beautiful and gently blurred, this next image somehow resembled a shallow stream. Clear water rippled over sunlit pebbles and water plants, long streamers of which gently swayed in the movement of the water. Sunlight flickered gently over everything—in many ways, a surprisingly realistic image. (G) This very powerful yet momentary image occurred towards the end of the operation. The incandescent green cross burned powerfully like an electric filament … an inspection light perhaps?

Figure 3 (A) After an initial period of impenetrable “fog”, the gas bubble gradually receded so as to allow me to see over the top of it. In these illustrations the bubble has receded to roughly halfway down the field of vision and I am lying on my left hand side with both eyes closed. The room is only semi-darkened. The pink light is very beautiful and emanates from a tiny convexity in the upper edge of the gas bubble. (B) The room is in complete darkness. The display is even more beautiful. Now it is a tiny concavity in the upper surface of the bubble that allows the violet “flare” of light to emerge.

Apolipoprotein E polymorphism in patients with cataract

Based on similarities in epidemiology and biochemistry, it has been suggested that cataract and Alzheimer’s disease (AD) share the same aetiological mechanisms. Comorbidity of cataract and AD in trisomy 21 (Down’s syndrome) is well known12 and both diseases are characterised by aggregated proteins exhibiting excessive glycation and racemisation of aspartyl residues.1 Several AD
related proteins—amyloid precursor protein (APP), β amyloid (Aβ), and presenilin (PS)—are expressed in the lens and Aβ is accumulated in the cytosol of lens fibres in cataractous lenses of people with AD.

Human apolipoprotein E (apoE) exists in three major isoforms encoded by distinct alleles (APOE ε2, ε3, and ε4). The different APOE alleles have been studied in relation to several human age related diseases: inheritance of the ε4 allele is a strong risk factor for AD and influences Aβ metabolism. The purpose of this study was to investigate the APOE ε2/ε3/ε4 polymorphism in patients with cataract.

After informed consent, patients with senile cataract and control individuals were recruited from two ophthalmic clinics in Tartu and the south Estonian area. The study was approved by the ethics committee at the University of Tartu, Estonia. Before surgery, the type of cataract was determined using biomicroscopy and ophthalmoscopy. Secondary cataracts were excluded. The case group included 502 patients; 77 with nuclear, 155 with cortical, 119 with posterior subcapsular, and 151 with mixed opacities. Mean age was 72.0 (SD 8.7) years (range 47–93 years) and 348 (69.3%) were women. The control group consisted of 187 individuals without cataract, uveitis, or glaucoma. Mean age was 65.8 (SD 6.9) years (range 43–90 years) and 136 (72.7%) were women. The age matched control group consisted of 187 individuals and 136 (72.7%) were women. The study recruited from two ophthalmic clinics in Tartu and the south Estonian area. The study was approved by the ethics committee at the University of Tartu, Estonia. Before surgery, the type of cataract was determined using biomicroscopy and ophthalmoscopy. Secondary cataracts were excluded. The case group included 502 patients; 77 with nuclear, 155 with cortical, 119 with posterior subcapsular, and 151 with mixed opacities. Mean age was 72.0 (SD 8.7) years (range 47–93 years) and 348 (69.3%) were women. The control group consisted of 187 individuals without cataract, uveitis, or glaucoma. Mean age was 65.8 (SD 6.9) years (range 43–90 years) and 136 (72.7%) were women. The power of the study was 99% as calculated according to Altman’s formula on the basis of APOE ε4 allele frequencies in a recent study on AD. The APOE alleles and genotypes were determined as previously described. The allele and genotype frequencies of cataract cases and controls were compared using a two tailed Fisher’s exact test, and odds ratios were calculated. All statistical analyses were performed using STATA as software. Statistical significance was defined as p<0.05.

APOE allele and genotype frequencies found in this study are well in accordance with those reported in other Northern European populations. No significant differences were seen between the control and cataract groups for any of the APOE alleles (table 1) or APOE genotypes (table 2). Neither were there any differences between the control group and the specific cataract subgroups. In order to prevent the data from being influenced by age differences between the groups studied, age matched control individuals were selected and compared with the cataract group and vice versa, without resulting in any significant changes in APOE allele or genotype frequencies.

Alzheimer’s disease and cataract both exhibit large aggregates of aberrant proteins, senile plaques composed of Aβ and neurofibrillary tangles containing the cytoskeletal protein tau in the former case, and light scattering high molecular weight aggregates of crystallins in the latter. Together with several other diseases characterised by protein aggregates, such as amyloidosis and prion diseases, the term “conformational disease” has been created, suggesting a common aetiology. The APOE ε4 allele is a strong risk factor for AD, and it is believed that in neuronal tissue, apoE is important for mobilisation and redistribution of lipids, and for maintenance and repair of neuronal cell membranes. However, in age related macular degeneration (AMD)—a condition characterised by accumulation of extracellular deposits termed drusen, containing among other things neutral lipids, cholesterol, and apoE—the ε4 allele appears to confer protection, whereas the ε2 allele is associated with a moderately increased risk of AMD. The APOE ε4 allele also seems to play a protective role during embryogenesis, suggesting different effects of the gene early and late in life.

To our knowledge, this is the first study to investigate the APOE polymorphism in cataract patients. No differences in the distribution of APOE alleles and genotypes could be seen between controls and cataract patients in spite of a large number of participants and a very high power. This indicates that if there is a common pathogenic mechanism for cataract and AD, it does not involve the groups studied, age matched control individuals were selected and compared with the cataract group and vice versa, without resulting in any significant changes in APOE allele or genotype frequencies.

Figure 4 (A) Considerable time has now elapsed and the gas bubble has diminished a great deal. This is my view of it with the eye closed and in strong sunlight. (B) This illustrates still further diminution of the bubble and its detachment from the edge of the field of vision. (C) Eventually the gas bubble became miniscule, and reversed its position in the visual field of vision before disappearing altogether.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>APOE allele frequencies for control and cataract groups</th>
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<tbody>
<tr>
<td>APOE allele</td>
<td>Controls (n = 374)</td>
</tr>
<tr>
<td>ε2</td>
<td>0.112</td>
</tr>
<tr>
<td>ε3</td>
<td>0.773</td>
</tr>
<tr>
<td>ε4</td>
<td>0.115</td>
</tr>
</tbody>
</table>

n, number of alleles. p<0.05 for all alleles when comparing controls and cataracts (all cases) or cataract subgroups. 95% confidence intervals of all odds ratios included 1.0 (no difference).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>APOE genotype distributions for control and cataract groups</th>
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<tbody>
<tr>
<td>APOE genotype</td>
<td>Controls (n = 187)</td>
</tr>
<tr>
<td>ε2/ε2</td>
<td>0.011</td>
</tr>
<tr>
<td>ε2/ε3</td>
<td>0.182</td>
</tr>
<tr>
<td>ε2/ε4</td>
<td>0.021</td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>0.588</td>
</tr>
<tr>
<td>ε3/ε4</td>
<td>0.187</td>
</tr>
<tr>
<td>ε4/ε4</td>
<td>0.011</td>
</tr>
</tbody>
</table>

p<0.05 for all genotypes when comparing controls and cataracts (all cases) or cataract subgroups. 95% confidence intervals of all odds ratios included 1.0 (no difference). NO, not observed.
APOE polymorphism. Of course the results need to be confirmed by other groups before the APOE polymorphism can be regarded as a significant in cataractogenesis. Bearing in mind the similarities between cataract and AD is very important, however, as progress in aetiological research of one disease may contribute to elucidating the pathogenesis of the other.

Acknowledgements
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References

Mitomycin C in sebaceous gland carcinoma with pagetoid spread
Sebaceous gland carcinoma is a rare eyelid tumour comprising less than 1% of all eyelid malignancies. It commonly arises from the meibomian glands of the tarsus, but may also arise from the glands of Zeis or from the sebaceous glands of caruncle. It can present in a nodular or diffuse infiltrative form. The latter form with intraepithelial (pagetoid) invasion has poor prognosis as a result of delay in diagnosis as well as more extensive involvement of ocular tissues. Topical application of mitomycin C, a non-cell cycle specific alkylating agent, has been advocated for pagetoid spread of sebaceous gland carcinoma. We report the use of mitomycin C as adjuvant therapy in a patient with completely excised sebaceous gland carcinoma and pagetoid spread.

Case report
A 78 year old man was referred to the oculoplastic clinic with epiphora and irritation of right eye for 2 years. There was no previous ocular or medical history. Clinically he had a unilateral right upper lid entropion with tarso-conjunctival cicatrisation (fig 1) and bilateral dermatochalasis. The patient underwent bilateral blepharoplasty and biopsy of right upper lid tarsal plate and conjunctiva. The biopsy confirmed sebaceous gland carcinoma with pagetoid invasion of the conjunctival epithelium (fig 2).

He had a full thickness wedge excision of the right upper lid with tarsocconjunctival biopsies. These showed sebaceous gland carcinoma to the margin of the excision with pagetoid invasion of the conjunctiva and epidermis of the lid margin. A wider excision of the lid and further conjunctival biopsies were performed with frozen section revealing complete excision of the tumour. Reconstruction of the posterior lamellae was achieved using a hard palate graft and the anterior lamella was repaired by a myocutaneous flap with post auricular skin graft and a bilobed flap mediawise.

Conjunctival map biopsies were clear of tumour 1 and 6 months post excision. In view of pagetoid spread, the patient was commenced on three cycles of topical mitomycin C 0.02% four times a day. Each cycle consisted of 2 weeks of mitomycin C and 2 weeks off therapy. Corneal epithelial toxicity and ulceration was noted with mitomycin C therapy, requiring preservative free lubricants and lateral tarsorrhaphy. Two years after excision of tumour, the patient remains disease free.

Comment
Intraepithelial invasion in sebaceous gland carcinoma is noted to occur in 41–80% of cases. Diagnosis may be delayed as the presenting symptoms are often benign and non-specific such as blepharoconjunctivitis. Diagnosis requires biopsy of the abnormal area and conjunctival map biopsies in the presence of intraepithelial invasion. Various treatments have been used for pagetoid invasion including surgical excision with cryotherapy, external beam radiotherapy, and orbital exenteration. Eyes with pagetoid invasion are more likely to undergo exenteration.

In our case the suspicion of malignancy was raised because of the unilaterality of the clinical features. Our patient underwent extensive excision of the tumour with tumour free conjunctival biopsies. Mitomycin C as adjuvant treatment was commenced as a result of the difficulty in clinically assessing for recurrence with pagetoid invasion. Mitomycin C was associated with moderate epithelial toxicity which was self limiting.

Mitomycin C is a non-cell cycle specific alkylating agent which acts to inhibit cell proliferation, and is used successfully in the treatment of corneal intraepithelial neoplasia. This is only the second reported article where mitomycin C has been used in the

Figure 1
Upper lid tarsal-conjunctival cicatrisation.

Figure 2
Conjunctival biopsy demonstrating intraepithelial invasion of malignant cells.
treatment of sebaceous gland carcinoma. In the pilot study by Shields et al.10 there was complete resolution of tumour with no recurrences over 12 month follow up. Mitomycin C as adjuvant treatment in pagetoid spread of sebaceous gland carcinoma may reduce the need for more invasive treatment options.

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A questionnaire survey of patient acceptability of optic disc imaging by HRT II and GDx

Glaucoma is an insidious condition which remains asymptomatic until very advanced with nerve damage occurring before detectable visual field loss.1 Early detection and treatment result in a better prognosis with retardation of progression.2

The Heidelberg retinal tomograph (HRT) II (Heidelberg Engineering, Germany) and the GDx Nerve fibre analyser (Laser Diagnostic Technologies Inc, San Diego, CA, USA) are instruments which use scanning laser technology to diagnose and monitor the progression of glaucoma. We conducted a questionnaire survey of subjects undergoing imaging by these methods in a primary care setting to compare patient acceptability of the two tests.

Methods
Seventy new patients referred with a possible diagnosis of glaucoma were asked to complete a questionnaire about their experience of optic disc imaging. Informed consent was obtained and the study had approval from the Moorfields Eye Hospital research and ethics committee. None of the subjects had undergone disc imaging previously. Subjects underwent sequential disc imaging by experienced technicians using HRT II then GDx or vice versa in approximately equal numbers. Only subjects who had vision of at least 6/12 and who had successful imaging by both methods were included.

The questionnaires consisted of two identical sets of six direct questions using a size 14 font (Appendix 1). Questionnaires were completed immediately after imaging to reduce the potential for recall bias. Statistical significance was determined using Binomial and McNemar’s tests.

Results
Sixty seven questionnaires were completed. Demographic and diagnostic data are shown in table 1 and patient responses in table 2. The majority of patients found both tests acceptable. Twenty eight (42%) subjects stated no preference for either imaging technique. Of the 39 subjects who did state a preference, 31 (79%) preferred HRT II compared with eight (21%) who preferred GDx (p = 0.009).

Most patients found both tests to be fairly acceptable. Twenty eight (42%) subjects stated no preference but of those who did, a significant proportion of patients preferred HRT II over GDx. The most common reason given was a shorter test duration implying that acquisition time may have an impact on acceptability. Examination with the GDx may be longer because of the external fixation target, which a greater proportion of subjects found difficult to focus on. In contrast the HRT II has an internal fixation target.

### Table 1 Demographic and diagnostic data

<table>
<thead>
<tr>
<th>Feature</th>
<th>(n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (50.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>33 (49.3%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean 57.1, SD 14.3, range 18–85</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Primary open angle glaucoma</td>
<td>12 (18%)</td>
</tr>
<tr>
<td>Glaucoma suspect</td>
<td>18 (27%)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>16 (24%)</td>
</tr>
<tr>
<td>Non-glaucomatous optic neuropathy</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>Normal</td>
<td>15 (22%)</td>
</tr>
<tr>
<td>No diagnosis given</td>
<td>3 (4.5%)</td>
</tr>
</tbody>
</table>

### Table 2 Patient responses

<table>
<thead>
<tr>
<th>Question</th>
<th>HRT</th>
<th>p Value (McNemar’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the test comfortable? (n = 65)</td>
<td>Yes 46</td>
<td></td>
</tr>
<tr>
<td>No 19</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>2. Was the light too bright? (n = 58)</td>
<td>Yes 2</td>
<td></td>
</tr>
<tr>
<td>No 26</td>
<td>0.3877</td>
<td></td>
</tr>
<tr>
<td>3. Was the chin rest uncomfortable? (n = 65)</td>
<td>Yes 19</td>
<td></td>
</tr>
<tr>
<td>No 26</td>
<td>0.0522</td>
<td></td>
</tr>
<tr>
<td>4. Was the test too long? (n = 65)</td>
<td>Yes 14</td>
<td></td>
</tr>
<tr>
<td>No 31</td>
<td>0.0039</td>
<td></td>
</tr>
<tr>
<td>5. Did you have trouble keeping your eye still? (n = 65)</td>
<td>Yes 3</td>
<td></td>
</tr>
<tr>
<td>No 62</td>
<td>0.0009</td>
<td></td>
</tr>
</tbody>
</table>

### References

Although the HRT II was found to be a more comfortable test, a higher proportion found the HRT II chinrest to be uncomfortable possibly because of the forward sloping angulation. We did not correlate patient preference with image acquisition time. More open questions may have helped to find the reasons for certain preferences. We were unable to determine the strength of preference from the collected data. Our study was also not randomised but roughly equal numbers had either HRT II or GDx first. We do not feel that there was a significant order effect. As our patients were new referrals, their responses were not biased by familiarity with previous tests. Patients underwent both tests sequentially on the same day by trained technicians reducing the likelihood of prolonged acquisition time due to inexperienced operators. All patients had good vision so locating the target was not an issue. Additional work examining the factors which affect acquisition time (for example, refractive error, presence of media opacity, pupil size) is needed to further understand patient preference. It is uncertain if the differences in preference between the two tests will have a significant impact on patient satisfaction and compliance with clinic visits as a whole. Other factors, such as waiting time and comfort of waiting room, will have to be examined as well.

In conclusion, our study highlights the importance of both test characteristics and comfort in instrument design. It is hoped that manufacturers take into account these factors in the design of the next generation of glaucoma imaging devices.

Appendix

1. The questions were:
   1. Was the test comfortable? Yes or No?
   2. Was the light too bright? Yes or No?
   3. Was the chin rests uncomfortable? Yes or No?
   4. Was the test too long? Yes or No?
   5. Did you have trouble keeping your eye still? Yes or No?
   6. (a) Which test did you prefer? HRT or GDx? (b) Why?

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A novel mutation in the alternative splice region of the PAX6 gene in a patient with Peters’ anomaly

The PAX6 gene is involved in ocular embryogenesis. This gene seems to be the master control gene for morphogenesis of the eye. Mutations in the PAX6 gene have been detected in various ocular anomalies suspected to have bilateral genetic backgrounds during development, including aniridia, Peters’ anomaly, foveal hypoplasia. In 1994, a sporadic case of Peters’ anomaly and a small family with a range of anterior segment malformations, including Peters’ anomaly, were shown to have a mutation of the PAX6 gene. More recently, Azuma et al reported a subject with Peters’ anomaly having a nonsense mutation in the alternative splice region of the PAX6 gene in 1999. Here we report a novel PAX6 gene mutation in a patient with Peters’ anomaly.

Case report

The present study had the approval of Kyoto Prefectural University of Medicine ethics committee and was conducted in accordance with the World Medical Association Declaration of Helsinki. Genomic DNA samples were isolated from the whole blood of patients and their relatives after informed consent. Each exon of the PAX6 gene and its immediate flanking sequence were amplified by polymerase chain reaction (PCR). Purified amplified fragments were subjected to sequenced using an ABI Prism 3100 genetic analyser (Applied Biosystems, Foster City, CA, USA). To confirm the sequence of mutations, the SNaPshot method was performed.

Of the four patients studied, we detected a novel missense mutation in one patient. The patient, a 20 year old girl, had bilateral Peters’ anomaly showing corneal opacity with iridocorneal adhesion and nystagmus (fig 1). The fundus of both eyes could not be seen because of corneal opacity. No systemic associations with Peters’ anomaly were identified. Sequence analyses revealed a heterozygous mutation as A>G at the 38th position which resulted in Q13R substitution in the PAX6 gene. No mutation was found in her parents and elder brother, which is consistent with the fact that they show no abnormal findings on clinical examination (fig 2).

Comment

We have identified one missense mutation in the alternative splice region (exon5a) of the PAX6 gene in a subject with Peters’ anomaly. This missense mutation was the substitution from glutamine to arginine at the 13th codon, which is the second reported position in the exon5a. The Pax family of developmentally regulated transcription factors share an amino terminal DNA binding motif known as the paired domain. The paired domain has a bipartite structure with a highly conserved N-terminal subdomain (NTS) and C-terminal subdomain, which bind distinctive consensus sequences, and the insertion of exon5a into

Figure 1 Photographs show the anterior segment region. (A) The anterior segment of the patient. She had bilateral Peters’ anomaly and showed corneal opacity with iridocorneal adhesion and nystagmus. The best corrected visual acuity was 20/100 (right) and 20/200 (left). The fundus of both eyes could not be seen because of corneal opacity. (B) The anterior segment of patient’s father. (C) The anterior segment of patient’s mother. (D) The anterior segment of patient’s elder brother. No congenital ocular abnormalities of anterior segment region were found in her parents or elder brother.
the N-terminal subdomain abolishes the DNA binding activity of the NTS.1
Interestingly, in 1999, Azuma et al proved that the mutation in the NTS of the paired domain partially restored the DNA binding activity of the NTS, using functional analyses.2 In addition, because the amino acids glutamine and arginine belong to hydrophilic and basic amino acid respectively, they have different electronic charges. Therefore, this amino acid substitution may affect the structure of the PAX6 protein and then change DNA binding activity of the paired domain. In other words, such a single amino acid substitution is an important motif as the paired domain such as we have found may severely damage the normal protein function. In fact, except for aniridia, other missense mutations that result in a serious congenital eye disease such as Peters’ anomaly or foveal hypoplasia, also exist in the paired domain. The typical clinical presentation with a missense mutation in a highly conserved and functionally important region suggests there is a reasonable likelihood that this sequence variant is caused by the patient’s phenotype. Our report adds a novel and potentially structurally significant mutation in the PAX6 gene to the present spectrum of mutations.

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with atypical presentations.1 This clinico-pathological report of a patient treated with immunosuppressive agents shows intraocular tuberculosis presenting with pigmented hypopyon.
A 38 year old female patient with a history of polyarthritis, anaemia, hypertension, and an impaired renal function with a possible clinical diagnosis of systemic lupus nephropathy underwent renal biopsy, which disclosed membranous glomerulonephropathy with peripheral granular deposits of IgG, Clq, and IgM on immunofluorescence. Her erythrocyte sedimentation rate was elevated (74 mm in the first hour) and she had positive antinuclear antibody; negative rheumatoid factor, VDRL, HIV, and tuberculin skin test (PPD). She was treated with intravenous cyclophosphamide 1 g per day once every month for 3 months and corticosteroids 30 mg/day. At the time of the third intravenous injection of cyclophosphamide, she noticed deterioration of vision in the right eye. On examination, right eye visual acuity was hand movements close to face. The conjunctiva was congested and the cornea was oedematous. The anterior chamber was shallow, and a 3 mm pigmented hypopyon was noted (fig 1). The left eye was unremarkable and the vision was 6/6. Blood and urine cultures showed no growth, and smears of anterior chamber fluid were negative for bacteria and fungi. Oral ciprofloxacin (500 mg twice per day) was started in addition to topical corticosteroids and mydriatics. A week later, the pigmented hypopyon had increased to 5 mm; it was aspirated and submitted for cultures and staining. Ziehl-Nielsen’s stain revealed several acid fast bacilli (AFB). The culture was positive for AFB and the Tuberculosis Research Centre in Chennai, India, identified the organisms as Mycobacterium tuberculosis based on pigment production, positive niacin, and catalase test. The patient was re-examined for evidence of systemic tuberculosis. Her PPD was negative and there were no radiological or clinical evidence of extraocular tuberculosis. Despite treatment with four antituberculosis drugs (rifampicin 450 mg, isoniazid 300 mg, ethambutol 800 mg, and pyrazinamide 1500 mg), and oral steroids (20 mg) for her polyarthritis, the patient developed multiple scleral abscesses and lost the remaining vision. She underwent enucleation of the right eye and was continued on antituberculous agents for 6 months. She was continued on tapering dose of systemic corticosteroids for 3 months following a fourth intravenous cyclophosphamide injection. She was followed for two more years and there were no signs of disseminated tuberculosis during that time.

Tuberculous intraocular infection presenting with pigmented hypopyon: a clinico-pathological case report
Tuberculosis still remains a major cause of morbidity and mortality today. Globally the incidence of this disease is increasing by eight million new cases annually and is a cause of death for two to three million patients every year.1 The ocular manifestations of tuberculosis are diverse, and depend on the immunological, bacteriological, and epidemiological variables.2 Individuals with compromised immune status usually present

Figure 1 The right eye shows oedematous cornea with presence of pigmented hypopyon.

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Histopathological examination of the enucleated eye showed infiltration of acute inflammatory cells and macrophages in the posterior half of the corneal stroma (fig 2). The anterior chamber was filled with pigment containing necrotic cells, macrophages, and proteinaceous exudate. The iris and ciliary body were necrotic and were infiltrated by pigment laden histiocytes. The sclera revealed necrosis with infiltration of acute inflammatory cells. The vitreous cavity contained proteinaceous exudate without significant inflammatory cell infiltration. Acid fast stains disclosed an abundance of AFB deep in the posterior half of the corneal stroma (fig 2).

Histopathological diagnosis was tuberculous necrotising keratouveitis.

Comment

In this case, the pigmented hypopyon was made up of melanophages. Darkly pigmented hypopyon may appear in eyes harbouring necrotic uveal melanomas in endogenous endophthalmitis caused by Listeria monocytogenes and Serratia marcescens.1,2 The cause of dark hypopyon in the endophthalmitis cases was assumed to be a dispersion of melanin from the necrotic iris. This way case also showed necrotic iris and dispersed melanin granules in the anterior chamber, suggesting a common underlying pathology for the formation of pigmented hypopyon. To the best of our knowledge this is the first known case of pigmented hypopyon in a biopsy and culture proved intraocular tuberculosis, and highlights the need for anterior chamber fluid analysis in arriving at the diagnosis.

The clinical spectrum of ocular tuberculosis infection includes chronic uveitis, interstitial keratitis, scleritis, sclerouveitis, optic neuritis, choroiditis, retinitis, chorioretinitis, and panophthalmitis.3,4 Hypopyon is rarely noted in tuberculosis. Ni et al presented cases of intraocular tuberculosis with turbid, haemorrhagic, greyish yellow exudate in the anterior chamber in one case, and fibrinous hypopyon in three other cases.5 Hypopyon may appear in rifabutin treated patients who had Mycobacterium avium complex infection.6 In all instances, the hypopyon was not darkly pigmented. The clinical and histopathological features suggest that the ocular infection could be endogenous; however, systemic evaluation did not disclose extraocular focus. The presence of large numbers of acid fast organisms in the histological sections suggest that the organisms could be atypical mycobacteria. However, the cultures showed that the organisms were Mycobacterium tuberculosis. Presence of such large numbers of the organisms in the ocular tissue could be from treatment induced immunosuppression.7

Acknowledgements

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Spontaneous stabilisation of symptomatic schisis detachments

Acquired retinoschisis affects 7% of people aged >40 years and is bilateral in 85%.1,2 Although retinoschisis is generally asymptomatic and stable, retinal detachment can supervene in one of three ways. Two of these are rare, are associated with posterior vitreous detachment (PVD), and justify surgical correction; thus, a retinal tear and detachment may originate within non-sclerotic retina or open breaks in the inner leaf of a schisis may allow fluid vitreous to be recruited into the cyst and thence to pass through breaks in the outer leaf, causing it to separate from the retinal pigment epithelium (RPE) over a wide area. The third mechanism—“schisis detachment”—is quite common (for example, 9% of cases of retinoschisis in one series).3

In March 2000 a 46 year old man was referred with a 2 day history of photopsia and a disturbance in the upper part of the visual field in his right eye. Visual acuity was 6/5 in each eye and there were no significant anterior segment abnormalities. Visual acuity was 6/8 in each eye and there was a PVD in the right eye. The patient had no history of intraocular surgery and no recent ocular trauma.

Photopsia initially improved and then reappeared, and at the next visit the right eye had a PVD. Funduscopy revealed a schisis detachment inferiorly in the right eye with a curvilinear outer leaf break at the posterior limit of the cyst (fig 1A). The detachment extended midway between the viscous nature of the vitreous and the anterior leaf of the schisis.

Retinoschisis cavities are commonly located to the temporal branch retinal artery and the fovea. The full thickness of retina delineating the superotemporal edge of the outer leaf break had a sauteweed pattern of outer retinal fibrosis, while the frontal edge of the break was rolled over. The oedema resolved within a week and no surgical intervention was recommended, merely observation. A bullous inferotemporal retinoschisis was also noted in this eye, extending almost to the major vascular arcade (fig 1B). During 3 years of follow up, a clinically obvious decrease in the height of the cyst and spontaneous closure of the outer leaf break were observed in the right eye. The PVD opacified indicating the extent of previous retinal detachment (fig 1C and E). Right vision has remained 6/5 albeit with visual field loss superiorly.

In November 2001, photopsia and visual field disturbances were experienced in the left eye. Examination revealed a curvilinear outer leaf break at the posterior limit of the inferotemporal cyst (fig 1D). The associated schisis detachment encroached upon, but did not involve, the left fovea. Given the patient’s history, surgery was considered unnecessary. Again the retinoschisis cavity deflated and subretinal fluid slowly absorbed leaving RPE atrophy and ventral cyst formation (fig 1F). Left vision has remained 6/5 but with an absolute superonasal scotoma.

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Comment

Most outer leaf breaks develop well within the confines of a retinoschisis, and cyst fluid separates the RPE and outer leaf only in the immediate vicinity of the breaks. However, the giant outer leaf breaks responsible for the schisis detachments in our patient were each located at the posterior limit of a large retinal cyst. It is unsurprising, therefore, that the detachments progressed beyond the retinoschisis and were symptomatic.

This is the first report of symptomatic schisis detachments that settled without surgery. We agree with Byer’s belief that the appropriate management for non-progressive schisis detachments is “to do nothing,” and the policy can be extended to symptomatic, inferior schisis detachments that do not involve the fovea. Surgical intervention, including retinopathy around the breaks, might well have induced sight threatening complications in our patient while offering no real prospect of a better outcome or prognosis.

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MAILBOX

Trypan blue: authors’ reply

We would like to thank Dr Rodrigues and colleagues for bringing up this interesting point of what exactly trypan blue stains.

In our study, immunohistochemistry was performed to determine the nature of cells involved in the epiretinal membranes (ERM) —not to determine the presence or absence of the ERM. Presence or absence of ERM was determined by examining routinely stained sections (haematoxylin and eosin, periodic acid Schiff) for cytoplasm/nuclei of epiretinal cell elements. All four of the macular hole internal limiting membrane (ILM) specimens were examined in this way. Furthermore trypan blue (in low concentrations) stains the anterior lens capsule. Since this capsule lacks glia, we do not believe that the evidence supports the contention of the correspondents that the staining of our ILM specimens is due to undetected “glial cell elements of the highly cellular ERM” rather than ILM.

Clinically two features are observed with the use of trypan blue. Firstly, the whole posterior pole that comes into contact with trypan blue is stained a faint blue in all cases. The staining pattern is diffuse and not patchy, suggesting trypan blue staining is indiscriminate of ERM or ILM. Secondly, in cases of macular pucker, the trypan blue stained ERM can be removed separately, leaving intact ILM behind, which can be further stained and removed. In cases of macular hole where a clinical ERM is not present, it appears that only the ILM is stained and peeled. We have harvested these membranes and confirmed that the membranes only consist of ILM and without a secondary ERM.

There is no doubt that trypan blue stains both ERM and ILM. We, however, have no knowledge as to what the structural elements of these membrane that the dye is attached to. We concede that staining of ILM with trypan blue can be variable and sometimes rather faint. Since our publication, Perrier and Sebag have also reported their experience with trypan blue in staining ILM and ERM.

Although histological findings were not given in these studies, clinically the authors found the dye to be useful in both types of membranes. Given the many concerns regarding the use of indocyanine green, we believe it is a positive development that an alternative clinically useful dye is available.

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Indeed, bilateral advanced visual field defects the cause of visual impairment and bilateral loss secondary to glaucomatous damage. Impairment may have been due to visual field occurring with age; therefore, age is not a factor in children following profound visual loss. This is documented in cases of acquired deafness. Interestingly, and supportive of this theory, evoking as an integral causative factor in CBS. The prevailing theory suggests sensory visual deprivation as an integral causative factor in CBS. The high incidence in the elderly population is possibly attributable to the increased incidence of acquired visual loss occurring with age; therefore, age is not a criterion for diagnosis. Further, although the Snellen acuity of all four patients was reasonably good in at least one eye of each patient, it may be surmised that severe visual impairment may have been due to visual field loss secondary to glaucomatous damage. Although this is not clear from the article, the cause of visual impairment and bilaterality are important in the diagnosis of CBS. Indeed, bilateral advanced visual field defects induced by glaucoma and homonymous hemianopia have resulted in CBS. The prevailing theory suggests sensory visual deprivation as an integral causative factor in CBS. Interestingly, and supportive of this theory, musical pseudohallucinations have been documented in cases of acquired deafness. Sensory deprivation in the presence of a clear sensorium will be necessary bilaterally to induce CBS, although no lower limit of Snellen visual acuity has been defined as a level for which CBS symptoms are stimulated. In the article case 4 seems to have sufficiently adequate visual function in the right eye to justify a definite misdiagnosis of CBS.

Secondly, as mentioned by the authors, Agarwal et al. have shown to cause systemic and neuropsychiatric phenomena. As with the discontinuation of any medication, the expectation would be resolution of induced symptoms. As we believe the hallucinations may easily be explained as a side effect of the medication. Bromodine is a known lipophilic compound able to penetrate the blood-brain barrier. Through the accompanying package insert, note side effects such as depression and dizziness are well known. There is, therefore, little doubt that in the aged population in whom pharmacokinetics is often unpredictable, the likelihood of systemic and neuropsychiatric phenomena and distribution may well lead to neuropsychiatric phenomena. Consequently, we believe that CBS was not the cause of the complex visual hallucinations experienced by these patients but may be attributed to a rarer side effect of bromodine, which should now be included in the patient information leaflet.

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Periocular corticosteroid therapy: comments

I read with great interest the article by Okada et al. reporting the efficacy and complications of trans-tenon’s retrobulbar infusion of triamcinolone acetonide for posterior uveitis. Sensory deprivation in the presence of a clear sensorium will be necessary bilaterally to induce CBS, although no lower limit of Snellen visual acuity has been defined as a level for which CBS symptoms are stimulated. In the article case 4 seems to have sufficiently adequate visual function in the right eye to justify a definite misdiagnosis of CBS. Interestingly, and supportive of this theory, musical pseudohallucinations have been documented in cases of acquired deafness. Sensory deprivation in the presence of a clear sensorium will be necessary bilaterally to induce CBS, although no lower limit of Snellen visual acuity has been defined as a level for which CBS symptoms are stimulated. In the article case 4 seems to have sufficiently adequate visual function in the right eye to justify a definite misdiagnosis of CBS.

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Howarth procedure

We read the article by Lai et al. regarding mucoceles: a comment on the management of frontoethmoidal mucoceles. It is mentioned that the transcaruncular approach for the treatment of frontoethmoidal mucoceles has been an accepted treatment for non-obliterative external procedures. It reduces blood-retinal barrier breakdown due to retinal photoacoagulation. Am J Ophthalmol 1992; 110:1155-9.


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Transcaruncular approach for the management of frontoethmoidal mucoceles: a comment

We read the article by Lai et al.’s interest. The authors report a modification of the non-obliterrative external procedure that was first described by Lynch in 1921. The Lynch-Howarth procedure2 involved transnasal stenting to prevent medial-ward collapse of the orbit obstructing drainage from the frontal sinus into the nose. Although the transcaruncular procedure uses a different external approach, it nevertheless often involves removal of part of the lamina papyracea for access to the sinuses. Hence, as with the Lynch approach, prolapse of orbital contents into the defect may occur, increasing the risk of re-stenosis. In addition, the cells in the frontal recess are not formally cleared and thus drainage into the nasal cavity is not assured. Stenting of sinus openings results in a significant fibrotic reaction in a proportion of patients, and closure of such a previously stented opening is likely. Furthermore, the follow up period in this study is too short to confirm the success or failure of this technique as recurrence often takes years to manifest.4 Endoscopic management of mucoceles protruding into the other sinuses or nasal cavity has been an accepted treatment for years.2 Frontoethmoidal mucoceles are typical of such mucoceles where the bony wall surrounding the mucocele is thin and therefore easily accessible transnasally. The endoscopic procedure creates a large area clear of cells which allows the greatest possible marsupialisation of the mucocele. No stenting is required. Har-El1 reported the largest series of 108 mucoceles with a median follow up of 4.7 years with a recurrence rate of only 0.9%. Therefore, we would recommend an endoscopic approach for frontoethmoidal mucoceles as the integrity of the lamina papyracea is maintained and the largest possible opening is created into the mucocele, which in turn minimises the chances of recurrence.

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NOTICES

Cataract surgery

The latest issue of Community Eye Health (No 48) discusses a solution to reduce worldwide cataract blindness, including suturesure non-phaco cataract surgery. For further information please contact: Journal of Community Eye Health, 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; website: www.jceh.co.uk). Annual subscription (4 issues) UK£28/US$45. Free to developing country applicants.

Elimination of avoidable blindness

The 56th World Health Assembly (WHA) considered the report on the elimination of avoidable blindness (doc A56/26) and urged Member States to: (1) Commit themselves to supporting the Global Initiative for the Elimination of Avoidable Blindness by setting up a national Vision 2020 plan by 2005; (2) Establish a national coordinating committee for Vision 2020, or a national blindness prevention committee to help implement the plan; (3) Implement the plan by 2007; (4) Include effective monitoring and evaluation of the plan with the aim of showing a reduction in the magnitude of avoidable blindness by 2010; (5) To support the mobilisation of resources for eliminating avoidable blindness. The WHA also urged the Director General to maintain and strengthen WHO’s collaboration with Member States and the partners of the Global Initiative for the Elimination of Avoidable Blindness as well as aid in the coordination and support of national capability.

XVth Meeting of the International Neuro-Ophthalmoogy Society


4th International Congress on Autoimmunity

The 4th International Congress on Autoimmunity will take place 3–7 November 2004 in Budapest, Hungary. The deadline for the receipt of abstracts is 20 June 2004. Further details: Kenes International Global Congress Organisers and Association Management Services, 17 Rue du Cendrier, PO Box 1726, CH-1211 Geneva 1, Switzerland (tel: +41 22 908 0488; fax: +41 22 732 2850; email: autoim04@kenes.com; website: www.kenes.com/autoim2004).

XVI International Congress for Eye Research

Mitomycin C in sebaceous gland carcinoma with pagetoid spread

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