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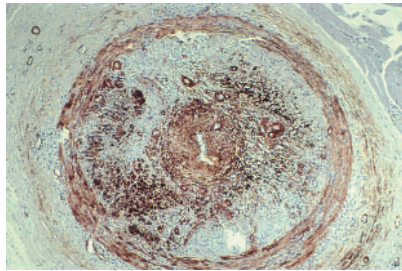
## LETTERS

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**Figure 1** Photomicrograph of temporal artery biopsy histological section shows a marked proliferation of smooth muscle cells that can be seen as dark reddish/brown concentric rings in the thickened medial and intimal layers (stain, actin which is selective for smooth muscle cells, original magnification,  $\times 250$ ).

### Heparin therapy in giant cell arteritis

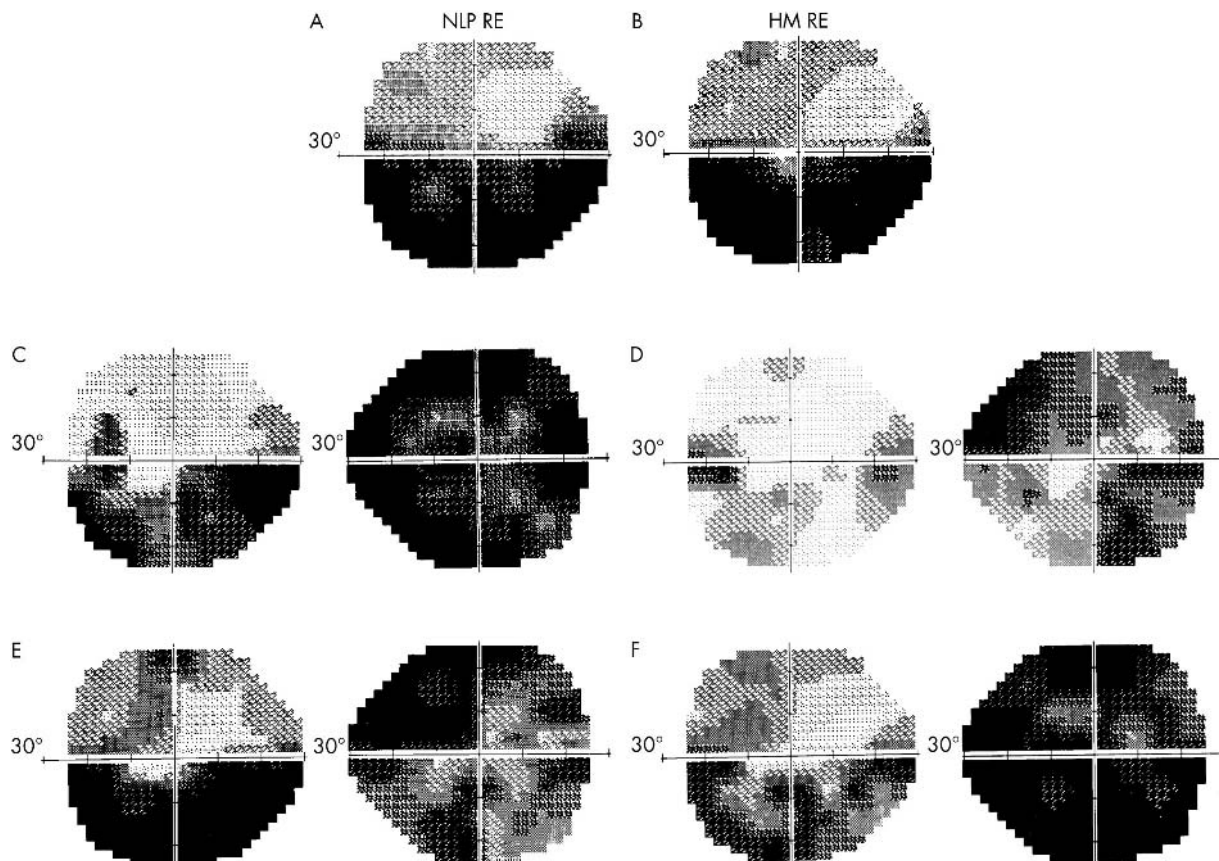
Giant cell arteritis (GCA) is a systemic vasculitis that affects large and medium sized arteries. Visual loss is one of the most

devastating complications of GCA and usually occurs from occlusion of the posterior ciliary arteries (PCA) leading to anterior ischaemic optic neuropathy (AION). Visual loss can also occur from occlusion of other arteries that supply the visual pathway, such as the central retinal and ophthalmic arteries.

Corticosteroid therapy, given orally or intravenously, is the standard treatment for GCA associated visual loss.<sup>1</sup> The optimal route of administration and dosage to prevent further visual loss are not known; however, most clinicians advocate higher doses in patients who already have experienced visual loss. Treatment with corticosteroids usually results in stabilisation of visual loss and some patients may have some degree of visual recovery.<sup>2,3</sup> However, despite treatment with high dose intravenous corticosteroids, visual loss may progress.<sup>1</sup> The reported use of adjunctive agents under these circumstances has been limited. We report a patient who had progressive visual loss while on high dose intravenous corticosteroids and who markedly improved after treatment with heparin.

### Case report

An 85 year old man presented to his optometrist for a routine eye examination. His visual acuity was 20/40 both eyes and his optic discs were normal. Three weeks later (day 1), he lost vision in his right eye. His visual acuity was now 20/100 right eye and 20/40 left eye. On visual field testing with



**Figure 2** Serial automated static perimetry, (A) Day 5: mean deviation (MD) =  $-19.63$  dB left eye, no light perception (NLP) right eye. (B) Day 6: MD =  $-17.99$  dB LE, hand motion (HM) right eye. (C) Day 7: MD =  $-12.30$  dB left eye, MD =  $-24.60$  dB right eye. (D) Day 8: MD =  $-5.58$  dB left eye, MD =  $-15.66$  dB right eye. (E) Day 9: MD =  $-17.63$  dB left eye, MD =  $-19.66$  dB right eye. (F) Week 4: MD =  $-12.80$  dB left eye, MD =  $-26.87$  dB right eye.

static perimetry he had an inferior altitudinal defect in the right eye and his visual field was normal in the left. His right optic disc was pale and oedematous and his left optic disc was normal. He was suspected of having GCA and was admitted for treatment with intravenous methylprednisolone (IVMP) 250 mg every 6 hours. On day 2, the visual field defect moved upward with involvement of fixation and his visual acuity was counting fingers. On day 3, the visual field defect increased further with a small rim of vision remaining superiorly. On day 4, his visual acuity was light perception (LP) and he was transferred to our institution.

On our initial examination (day 4), his visual acuity was LP right eye and 20/50 left eye. He had a right relative afferent pupillary defect (RAPD), pale optic disc oedema on the right, and a normal appearing optic disc on the left. The Westergren erythrocyte sedimentation rate (ESR) was 74 mm in the first hour. The IVMP was continued as before, and a temporal artery biopsy (TAB) was performed which was positive for GCA (fig 1).

On day 5, his visual acuity decreased to no light perception (NLP) right eye and 20/80 left eye. His right pupil was amaurotic and his left pupil reacted sluggishly. Static perimetry now showed an inferior altitudinal defect in the left eye (fig 2A). The right optic disc appearance was unchanged but the superior portion of the left optic disc was now pale and oedematous. Posterior ciliary artery (PCA) blood flow could not be detected in either eye with orbital colour Doppler imaging (CDI) (table 1). Heparin (5000 units intravenous bolus) was started, and titrated to maintain the partial thromboplastin time (PTT) within a therapeutic range (46–70 seconds).

On day 6, his PTT was 74 seconds and his visual acuity improved to hand motion (HM) right eye and 20/70 left eye. His right pupil reacted sluggishly and the left pupil reacted more briskly with a right RAPD. Static perimetry was essentially unchanged (fig 2B) and there was no appreciable change in the optic disc appearance. The ocular blood flow characteristics with orbital CDI (fig 3A) were unchanged (table 1).

On day 7, while continuing IVMP and heparin, his visual acuity improved to counting fingers (CF) at 1 foot right eye and 20/50 left eye. The pupillary examination was unchanged. Static perimetry was improved (fig 2C). Posterior ciliary artery blood flow

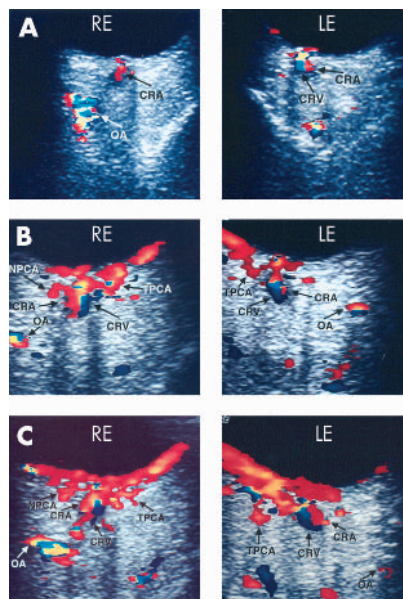
was now detectable with orbital CDI (table 1). Warfarin (2.5 mg by mouth four times daily) was added and titrated to a therapeutic level. By day 8, his visual acuity had improved to 20/400 right eye and 20/50 left eye. Static perimetry was further improved (fig 2D). The ocular blood flow characteristics on orbital CDI likewise improved (table 1). The pulsatility index of the central retinal artery (CRA) was markedly decreased (fig 4). Oral corticosteroid therapy (prednisone 100 mg by mouth daily) was started and IVMP therapy was stopped.

On day 9, the international ratio (INR) was therapeutic (between 2 and 3) and heparin was stopped. His visual acuity was 20/200 right eye and 20/70 left eye. Static perimetry was slightly worse in the right eye and the inferior altitudinal defect in the left eye was

denser and closer to fixation (fig 2E). The ocular blood flow characteristics on orbital CDI (fig 3B) remained stable (table 1). The patient was discharged from the hospital with oral corticosteroid therapy (prednisone 100 mg by mouth daily) and warfarin.

At the 1 week follow up visit (day 15), his visual acuity improved to 20/80 right eye and 20/40 left eye. Static perimetry was unchanged. The ocular blood flow characteristics on orbital CDI (fig 3C) remained unchanged (table 1).

At the 4 week follow up visit while taking 100 mg of prednisone daily and warfarin, his visual acuity deteriorated to 20/400 right eye and 20/80 left eye. Static perimetry worsened in the right eye with diffuse loss and the inferior altitudinal defect left eye was less dense (fig 2F). The ocular blood flow



**Figure 3** Serial orbital colour Doppler imaging. (A) Day 6: There is diminished blood flow through the ophthalmic artery (OA) in the right eye (OD) and central retinal artery (CRA) in both eyes. The blood flow through the posterior ciliary artery circulation is undetectable in both eyes. Blood flow through the central retinal vein (CRV) can be seen in the left eye (OS). (B) Day 9: 4 days after starting heparin, there is blood flow through the nasal posterior ciliary artery (NPCA) OD and through the temporal posterior ciliary arteries (TPCA) both eyes, with improved blood flow through the OA and CRA in both eyes. Blood flow through the CRV can be seen in both eyes. (C) Day 15: 6 days after discontinuation of heparin, the ocular blood flow remained stable.

**Table 1** Spectral analysis of orbital colour Doppler imaging

	Normal values <sup>11</sup> (cm/s)	Day 5		Day 6		Day 7		Day 8		Day 9		Day 15	
		RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE
CRA systolic (cm/s)	10.1+/-1.9	4.1	2.4	5.4	4.7	5.3	4.5	5.9	4.4	8.2	5.6	9.7	5.7
CRA diastolic (cm/s)	2.6+/-1.2	0.2	0.4	0.4	0.6	1.3	1.4	1.6	0.7	2.4	1.6	3.0	1.7
CRA pulsatility index	1.52	20.0	6.3	49.0	8.2	42.0	32.0	3.9	4.2	1.0	2.0	2.8	1.87
PCA systolic (cm/s)	12.4+/-4.2												
Nasal		NR	NR	NR	NR	4.2	NR	5.1	NR	7.7	NR	8.0	NR
Temporal		NR	NR	NR	NR	3.1	7.2	4.8	9.1	7.4	9.4	7.4	5.0
PCA diastolic (cm/s)	4.3+/-2.2												
Nasal		NR	NR	NR	NR	0.8	NR	0.4	NR	2.6	NR	2.3	NR
Temporal		NR	NR	NR	NR	0.5	1.3	1.2	0.2	2.3	0.2	2.7	1.7
PCA pulsatility index	1.09												
Nasal		NR	NR	NR	NR	1.8	NR	1.0	NR	1.3	NR	2.0	NR
Temporal		NR	NR	NR	NR	7.7	3.0	3.1	3.9	1.7	2.2	1.9	3.0
OA systolic (cm/s)	31.3+/-4.2	58.0	133.4	65.1	118.9	65.7	118.6	59.9	94.9	58.0	71.5	58.0	50.3
OA diastolic (cm/s)	8.3+/-3.9	19.3	31.9	16.9	37.7	21.3	16.9	19.3	23.7	23.2	11.6	20.3	10.3
OA pulsatility index	1.55	1.2	1.4	1.2	1.2	1.1	1.5	1.2	1.2	1.0	1.4	1.1	2.1

CRA = central retinal artery, PCA = posterior ciliary artery, OA = ophthalmic artery, NR = not recordable.

**Table 2** Review of five large series of visual outcome in GCA treated with either oral or intravenous corticosteroid therapy

Reference	Year	Total number of patients with GCA	Number of patients with visual loss	Number of patients (%) with visual stabilisation	Number of patients (%) with visual recovery	Number of patients (%) with progression of visual loss
Chan <i>et al</i> <sup>4</sup>	2001	73	73	43 (59)	21 (29)	9 (12)
Liozon <i>et al</i> <sup>7</sup>	2000	147	23	17 (74)	5 (22)	1 (4)
Gonzalez-Gay <i>et al</i> <sup>5</sup>	1998	239	34	22 (65)	8 (23)	4 (12)
Liu <i>et al</i> <sup>6</sup>	1993	45	41	20 (49)	14 (34)	7 (17)
Aiello <i>et al</i> <sup>8</sup>	1992	245	34	24 (70)	5 (15)	5 (15)

characteristics on orbital CDI remained unchanged. At the 3 month follow up visit while still on the same medications, his visual acuity deteriorated to LP right eye and improved to 20/60 left eye. Static perimetry of the left eye was unchanged and the ocular blood flow characteristics on orbital CDI again remained stable bilaterally. His prednisone dosage was slowly tapered and the warfarin was discontinued.

### Comment

Once visual loss occurs in GCA, the goals of treatment with corticosteroid therapy are to prevent further progression and to reverse the visual loss if possible. Table 2 reviews the treatment results of GCA with either oral or intravenous corticosteroid therapy in five large series of patients. After initiation of corticosteroid therapy, most patients experienced visual stabilisation, a small number had improvement of vision, and even fewer patients had a progression of visual loss.

The reason for progression of visual loss despite treatment with corticosteroid therapy is unknown. One possible reason is that the dose of corticosteroids was inadequate. Both the dose and route of administration of corticosteroids varied in the studies in table 2. Therefore, it is difficult to assess whether the treatment dose was adequate or if intravenous administration is superior to oral administration.

Most clinicians support the use of high dose intravenous corticosteroids for patients who have experienced visual loss from GCA. However, progression of visual loss has been described despite high dose IVMP.<sup>1-4-6</sup>

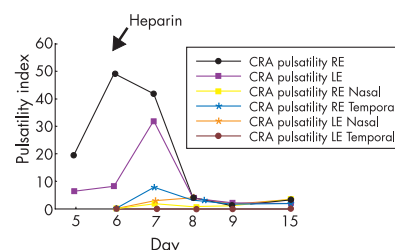
Another possible reason for the progression of visual loss despite treatment is that corticosteroid therapy alone is an inadequate treatment for some patients. A review of our patient's TAB showed near total luminal stenosis by intimal hyperplasia with proliferation of actin stained smooth muscle cells in the arterial media and intimal layers (fig 1). Complete arterial occlusion can occur with progression of the hyperplastic process or may be the result of superimposed arterial thrombosis. Perhaps with advanced luminal stenosis, corticosteroids are not as effective as they are early in the inflammatory cascade and may not be able to prevent thrombosis.

We found one report of the use of heparin for visual loss in GCA.<sup>7</sup> In a review of 174 patients with GCA, Liozon *et al* reported the use of heparin in most patients with permanent visual loss and some patients with threatening symptoms.<sup>7</sup> However, the specific results of this treatment were not reported. The use of heparin has also been described for manifestations of GCA other than visual loss. Staunton *et al* described a 64 year old man with TAB proved GCA and clinical signs of an evolving vertebrobasilar stroke and

ischaemic cerebellar lesion on MRI while on oral corticosteroid therapy.<sup>8</sup> His symptoms improved following treatment with high dose intravenous dexamethasone and heparin. It has been postulated that systemic anticoagulation may be beneficial during the initial phase of steroid treatment because of recent evidence that anti-cardiolipin antibodies are present in a higher frequency in patients with GCA.<sup>9</sup>

Normally, heparin occurs complexed to histamine as a macromolecule in mast cells and its physiological role is unknown. Heparin has an immediate anticoagulation effect after intravenous administration. The coagulation process generates thrombin by two interrelated pathways, the extrinsic and intrinsic. Both pathways involve a cascade of enzymatic reactions that ultimately form thrombin. Thrombin catalyses the conversion of fibrinogen to fibrin that forms the matrix of a thrombus. Thrombin also activates clotting factor XIII that is necessary for stabilising the cross links of the fibrin molecules. If thrombin is not produced or production is impeded then coagulation is inhibited. Antithrombin III is an  $\alpha$ -globulin that inhibits thrombin. Heparin indirectly binds to antithrombin III and forms a complex that more rapidly inhibits thrombin formation, thereby preventing coagulation and clot formation.

Heparin has also been shown to have other biochemical activities such as regulation of lipid metabolism, control of blood fluidity at the endothelial surface, control of cell attachment to various proteins in the extracellular matrix, binding with acidic and basic fibroblast growth factors, binding to interleukin 3 and granulocyte-macrophage colony stimulating factor, and inhibition of serotonin induced pulmonary artery smooth muscle cell hypertrophy.<sup>10</sup> The mechanism by which heparin led to improvement of vision in our patient is not known and perhaps its therapeutic effect was unrelated to anticoagulation. None the less, serial orbital CDI showed improvement in ocular blood flow (table 1; fig 3A-C). Colour Doppler imaging is an ultrasonic imaging modality that combines B-mode ultrasonography with Doppler ultrasonography. When applied to the orbit, this imaging modality allows for the assessment of ocular blood flow and has been described in detail elsewhere.<sup>11-12</sup> Blood flow towards the transducer is displayed as red and represents arterial flow and blood flow away from the transducer is displayed as blue and represents venous flow. Pulsed Doppler with spectral analysis can be used in conjunction with the CDI to accurately quantify the systolic and diastolic flow characteristics. The pulsatility index can be calculated and represents an assessment of vascular resistance to blood flow. A high pulsatility index



**Figure 4** Graph of arterial pulsatility index. Blood flow through the posterior ciliary artery (PCA) was detectable on day 7 and central retinal artery (CRA) pulsatility index was nearly normal by day 8.

indicates a high resistance and therefore reduced blood flow.

Initially, the systolic and diastolic pressures of the CRA were well below normal and the pulsatility index was markedly increased. The flow parameters of the PCA were undetectable. After heparinisation (day 5), flow was restored to the PCA circulation (day 7, table 1). The pulsatility index of the CRA also decreased (days 6-8, fig 4). The decrease in pulsatility index represents a decrease in blood flow resistance. The decrease in pulsatility index and restoration of blood flow to the PCA circulation both correspond to an improvement in visual acuity and visual field. The sequence of rapid improvement of orbital CDI haemodynamics, visual acuity, and visual field strongly suggest that the administration of heparin was responsible. Since this occurred rapidly, some of the biochemical activities of heparin, such as inhibition of smooth muscle cell hypertrophy and the others that act on a more chronic time line could not have caused improvement. A more likely candidate might be the control of blood fluidity at the endothelial surface.

In summary, the use of corticosteroid therapy alone for the treatment of GCA may have limited therapeutic success. The pathogenic mechanism of luminal stenosis in GCA is undergoing revision,<sup>13</sup> and the emerging model offers possibilities for novel therapeutic intervention. Our patient had a remarkable improvement in visual acuity within 24 hours after starting heparin. Over the ensuing 2 days his visual field and ocular blood flow improved. The improvement with the addition of heparin may have been coincidental, and his vision may have recovered with IVMP alone. However, the continued decline in visual function, despite 3 days of IVMP, and his dramatic improvement after starting heparin, strongly suggests that heparin had a pivotal role in his recovery.

At the 3 month follow up visit, his vision in the right eye deteriorated to LP, even though

his ocular blood flow characteristics were stable. We are uncertain about the reason for his decline in visual function, since at the time of the decline, he was maintained on oral corticosteroid and his serial ESR values were normal. None the less, we suggest that in patients who experience a progression of visual loss from GCA, despite IVMP therapy, may benefit acutely from the addition of heparin therapy.

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## Retinal migraine: caught in the act

A 22 year old male dancer presented via his optometrist following an episode of transient visual loss in his left eye. He described a slow blurring and darkening of the vision of the left eye with a similarly gradual return to normal, the whole episode lasting 10 minutes. He described similar episodes every 2–3 months for the previous 3 years with no associated migrainous aura or headache, and exercise was not a trigger. Figure 1 shows images taken before, during, and 10 minutes after his presenting episode (see figure legend for description).

Visual acuity was no perception of light when tested during the episode and had recovered to 6/9 in the affected left eye when seen 2 hours later at our ophthalmic emergency department. Aside from congenital protanomaly there were no other ocular or systemic abnormalities. On subsequent review his visual acuity had returned to 6/6 bilaterally and his fundus appearance remains normal. There was no visual field abnormality (Goldmann I2e, I4e) and haematological (including thrombophilia screen), carotid, and cardiac investigations were normal.

## Comment

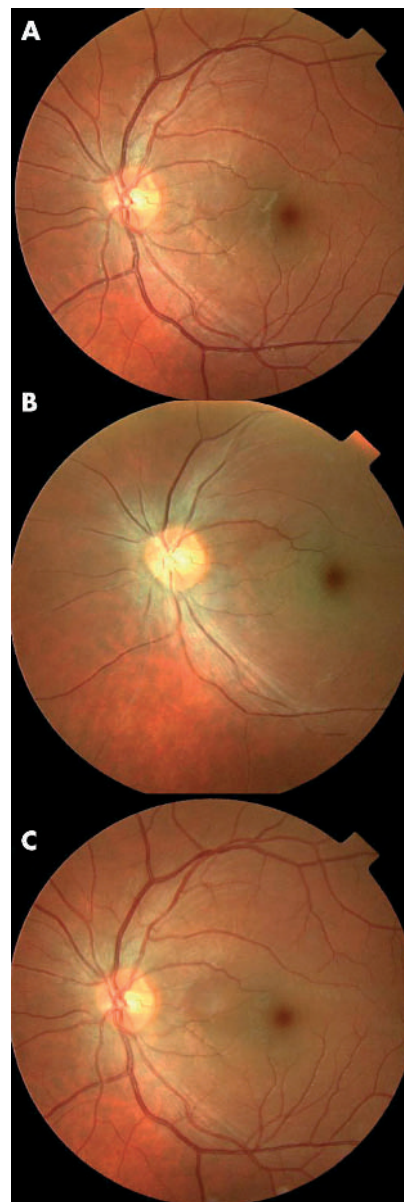
Retinal migraine (otherwise known as ophthalmic migraines, anterior visual pathway migraines, or ocular migraines) causes monocular visual loss for 10–20 minutes which can be associated with diffuse or unilateral headache.<sup>1</sup> People experiencing ocular migraines often have a history of one of the more conventional forms of migraine, and exercise may precipitate the attacks.<sup>2</sup> Vasospasm of the retinal circulation or ophthalmic artery is thought to be the cause of the amaurosis of ocular migraine.<sup>1–5</sup> Ischaemic optic neuropathy<sup>6</sup> and permanent arcuate scotomas<sup>3</sup> may occur after ocular migraine and retinal vascular occlusions have been reported in conjunction with cerebral<sup>7</sup> and ocular migraine.<sup>5,8</sup>

Retinal vasospasm may be associated with underlying systemic diseases such as SLE<sup>9</sup> and antiphospholipid syndrome.<sup>5,9</sup> In older patients it may be associated with giant cell arteritis, polyarteritis nodosa, and eosinophilic vasculitis.<sup>1</sup> Other associated haematological abnormalities include low protein C and S levels and positive antinuclear antibodies.<sup>5</sup>

A relative afferent pupillary defect can be demonstrated during episodes.<sup>4,10</sup> Retinal arterioles have been reported to constrict,<sup>1</sup> and the fovea may become more distinct<sup>1</sup> with surrounding macular retinal pallor<sup>4</sup> The optic discs may be pale<sup>1,2,5</sup> early and hyperaemic later.<sup>4,7</sup> Early isolated constriction of

veins has been reported,<sup>1,10</sup> which may be segmental,<sup>1</sup> as well as simultaneous constriction of arterioles and veins.<sup>2</sup> Later engorgement of the retinal veins has been observed some hours after an attack.<sup>7</sup> Nerve fibre bundle defects can sometimes be a late finding.<sup>3</sup>

Our case demonstrates photographically the arterial vasoconstriction of retinal migraine (fig 1), which occurred in the absence of a precipitating cause such as



**Figure 1** (A) Left eye taken at routine optometrist appointment 1 month before presenting episode; normal appearance of disc, vessels, and macula. (B) During the episode of visual loss, constriction of both arteries and veins is seen with macular pallor and a central cherry red spot and slight disc pallor. (C) 10 minutes after the previous picture when vision according to the patient had returned to normal. Some pallor remains in the macula with a central cherry red spot but the disc and vasculature have returned to normal.

exercise and in the absence of a migrainous aura or headache.

Doppler studies have revealed cessation of retinal arterial flow during an exercise induced retinal migraine episode.<sup>2</sup> A 48 year old cluster headache sufferer who underwent fluorescein angiography during an ocular migraine attack demonstrated narrowing of the retinal veins and delayed retinal artery filling during the episode with normal choroidal filling.<sup>10</sup> Most previously published photographs have shown venous, retinal, and disc changes late in the attack, perhaps reflecting that arterial vasoconstriction occurs early during attacks and is not often photographed.<sup>2,4,10,11</sup> Alternatively, there may be a spectrum of severity of retinal migraine manifestations, which in severe cases may result in a transient pale macular area with cherry red spot.

When considered necessary, effective treatments include propranolol,<sup>10</sup> verapamil,<sup>5</sup> and nifedipine.<sup>2,5</sup> Prophylactic aspirin or nifedipine may be tried to prevent exercise induced attacks,<sup>2</sup> and inhaled amyl nitrate can be used early in an attack to try to induce resolution.<sup>4</sup>

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## Long term follow up in a case of successfully treated idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN)

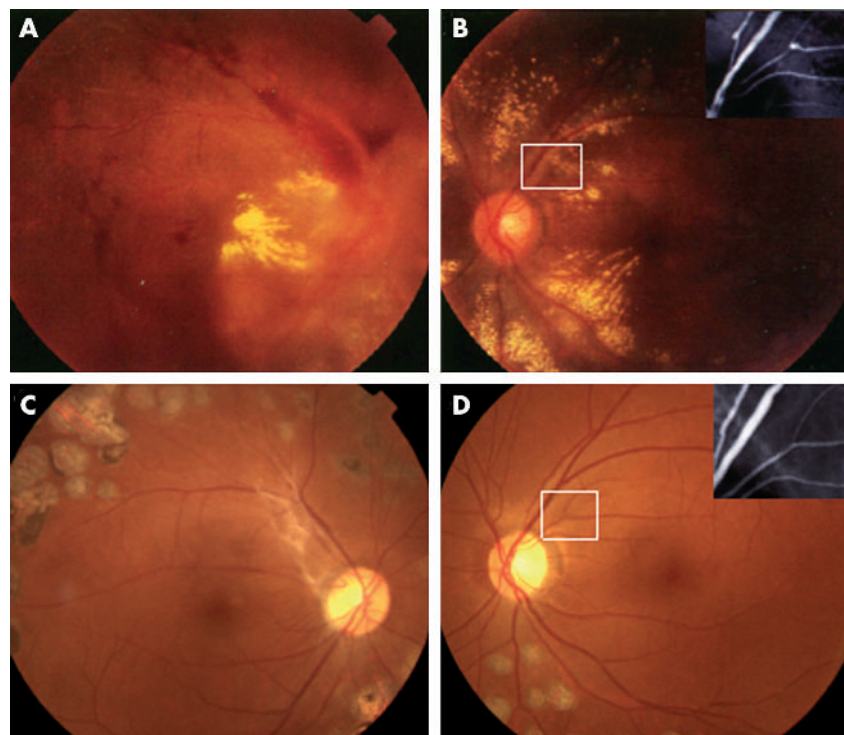
The idiopathic retinal vasculitis, aneurysm, and neuroretinitis (IRVAN) syndrome is a rare clinical entity characterised by peripheral retinal vascular occlusion, retinal vasculitis, and multiple posterior retinal arterial aneurysms.<sup>1,2</sup> In most reported cases, visual acuity was aggravated.<sup>2–4</sup> We report a case of successfully treated IRVAN syndrome in which good long term visual acuity has been maintained.

### Case report

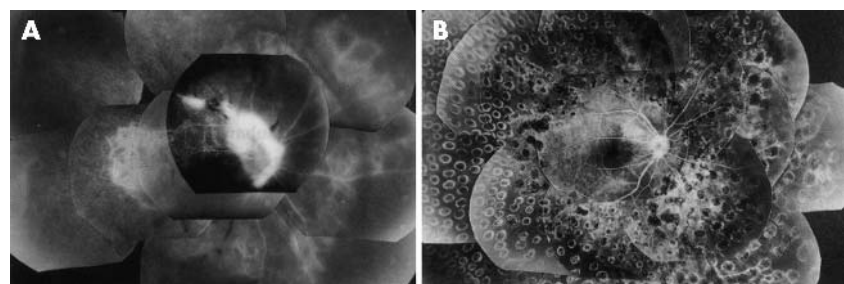
A 36 year old woman visited the Kansai Medical University Hospital on January 1999, complaining of flies flying in her right eye for the past year. She also had visual disturbance and metamorphopsia for 2 months in her right eye. Her best corrected visual acuity was

20/40 in the right eye and 20/16 in the left eye. Inflammatory cells were noted in both the anterior chamber and vitreous cavity. There was mild rubeosis iridis in the left eye. In the right eye, there was a fibrovascular membrane in the epipapillary area accompanying tractional retinal detachment, thick hard exudates on nasal side of the fovea, and vitreous haemorrhage (Fig 1A). Her optic disc was mildly hyperaemic, and multiple aneurysms surrounded by perivascular exudation were observed at the posterior retinal artery in the left eye (Fig 1B). Extensive arterial and venous vascular occlusion and adjacent anomalous arteriovenous anastomosis were observed at the peripheral retina in both eyes (Fig 2).

Systemic examination and laboratory findings did not suggest systemic abnormality, and the family history was not contributory. Oral prednisolone was initiated at 50 mg/day and decreased gradually. In an attempt to prevent peripheral retinal neovascularisation, panretinal photocoagulation (PRP) was car-



**Figure 1** Vitreous haemorrhage, neovascularisation of the optic disc, and hard exudates were observed in the right eye (A), and hard exudates surrounding the optic disc and aneurysms shown by fundus fluorescein angiogram (FA) was observed in the left (B) on January 1999. The right eye (C), and aneurysms shown by FA in the left (D) were improved by February 2003.



**Figure 2** Panoramic FA of the right eye on January 1999 (A) and February 2003 (B).

ried out to treat the peripheral retinal non-perfusion area. Since vitreous haemorrhage in the right eye did not improve, right eye vitrectomy was performed on March 1999, and tractional retinal detachment and vitreous haemorrhage subsequently improved. The aneurysms disappeared by 5 months and the hard exudates by 12 months. Her corrected visual acuity improved to 20/20 in the right eye and 20/16 in the left eye by February 2003 (Fig 1C and D).

**Comment**

The disappearance of retinal aneurysm in IRVAN has been reported in two cases.<sup>3,4</sup> In both of these cases, scattered retinal photocoagulation was performed on the peripheral retinal non-perfusion area.<sup>3,4</sup> In one case in which scattered retinal photocoagulation was not performed, it has been reported that some aneurysms enlarged, others became small, and new aneurysms appeared.<sup>5</sup> In our case, all retinal arterial aneurysms vanished after PRP (Fig 1B and D). These results strongly suggest that PRP applied to the retinal non-perfusion area is useful and should be performed during the early phase. On the other hand, it has been reported that retinal lesions are unresponsive to oral steroids in most cases of IRVAN.<sup>2,4,5</sup> In our case, systemic oral steroid was given to treat the retinal vasculitis. The effect of oral steroid in IRVAN will need further examination. The results in our case and past cases strongly suggest that PRP applied to the non-perfusion area is the most important treatment for IRVAN. We think vitrectomy must precede PRP, because PRP cannot be performed when there is vitreous haemorrhage and retinal detachment.

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**HLA typing is not predictive of proliferative diabetic retinopathy in patients with younger onset type 2 diabetes mellitus**

Chronic hyperglycaemia and the duration of diabetes are the most important factors in retinopathy. However, retinopathy progresses

in some patients despite good glycaemia control. Also, poor glycaemia control does not always lead to retinopathy in younger onset patients, while still others develop severe retinopathy that is resistant to retinal photocoagulation.

These facts suggest that the risk factors for diabetes and retinopathy are not necessarily the same, and that the development of severe retinopathy may be influenced by genetic factors.<sup>1</sup>

Human leucocyte antigen (HLA) status has a significant role in immune responses and immunological tolerance and is a factor in the onset of type 2 diabetes.<sup>2-4</sup> DR4, DR8, DR9, and several antigens of the DQ region are related to retinopathy in patients with type 1 diabetes.<sup>5,6</sup> In addition, it was reported that HLA-DR was expressed in proliferative retinopathy.<sup>7,8</sup> Little is known, however, about the relation between retinopathy with type 2 diabetes and the HLA antigen. Furthermore, most previous studies have not taken into consideration the background of glycaemic control or the duration of the diabetes. A group of younger onset type 2 diabetes patients with PDR, and a group who had no signs of retinopathy despite a long duration of diabetes were compared. Younger patients were studied to reduce the influence of adult diseases such as hyperlipidaemia and hypertension. In addition, clinical background factors were considered when studying the frequency of HLA types.

**METHODS**

Following the informed consent of each of the subjects, blood samples were collected. The study was approved by the human studies review board of Tokyo Women's Medical University and was performed in accordance with the Helsinki Declaration of 1975 and its 1983 revision. The diagnosis of type 2 diabetes was made based on 1985 World Health Organization criteria.<sup>9</sup> We excluded subjects who were GAD antibody positive. The patients had been diagnosed as having type 2 diabetes aged under 30 years

(range 12–21 years) and type 2 diabetes duration for more than 10 years. Additionally, the patients whose average HbA<sub>1c</sub> level over 10 years was from 6% to 10%, were selected in this study. All were receiving treatment at Tokyo Women's Medical University Diabetes Center.

Further, two groups were selected from above patients, as follows. The PDR group consisted of 44 patients, who had undergone vitreous surgery under the age of 40 (mean 28.8 (SD 4.4) years) where surgery had been carried out at the department of ophthalmology, diabetes centre (as above) during the period 1993–9. The non-DR group consisted of 45 patients who had no signs of retinopathy despite having diabetes for more than 10 years. Consequently, the sex, the diabetes duration, and the blood glucose control have been matched between the two groups on the basis of the selection criteria above (table 1). The control group selected for comparison, consisted of 50 healthy patients. The HbA<sub>1c</sub> level was determined with resin microcolumn technique (HPLC, Kyoto Chemical) (normal range 4.3–5.8%).

HLA-A, B, C, DR, and DQ typing of blood samples was conducted on all three groups using standard microcytotoxicity methods.

For comparisons between the groups, we applied the  $\chi^2$  test of independence or Fisher's exact probability test. The unpaired *t* test was used for comparing mean values. The level of significance was set at  $p < 0.05$ . All analyses were performed using the Stat View statistical software package (Abacus Concepts, Berkeley, CA, USA).

**RESULTS**

The frequencies of HLA-A, B, and Cw antigens in the control group, the non-DR group, and the PDR group are shown in table 2, and those of DR, and DQ antigens in table 3, respectively.

There was no significant difference among the three groups in HLA-A, B, and DQ antigens. The non-DR group showed higher frequencies of HLA Cw4 ( $\chi^2 = 4.027$ ,

**Table 1** Clinical profile of the control group, non-DR group, and PDR group

	Control group	Non-DR group	PDR group	p Value
Number of patients	50	45	44	–
Age (years)†	27.4 (2.7)	27.8 (2.8)	29.2 (4.1)	NS
Male/female	25/25	20/25	20/24	–
Age at the diagnosis of diabetes (years)	–	16.5 (4.3)	16.7 (3.7)	NS*
Age at the diagnosis of diabetic retinopathy (years)	–	–	21.6 (4.5)	–
Age at the time of vitreous surgery (years)	–	–	28.8 (4.4)	–
HbA <sub>1c</sub> (%)	–	7.7 (1.6)	7.9 (1.9)	NS*
Hypertension (%)	0 (0.0%)	3 (6.7%)	4 (8.3%)	NS**
Renal disease (%)	0 (0.0%)	6 (13.3%)	15 (34.1%)	.0021**
Neurophysiological neuropathy (%)	0 (0.0%)	9 (20.0%)	18 (40.9%)	.032**
Positive family history (%)	0 (0.0%)	15 (33.3%)	19 (43.1%)	NS**

Number of patients or mean (SD).

NS = not significant.

The age was compared between each group.

\*Comparisons between the non-DR group and the PDR group by unpaired *t* test.

\*\*Comparisons between the non-DR group and the PDR group  $\chi^2$  test of independence or Fisher's exact probability test.

†Age at the time of this study.

‡Average value over 10 years.

**Table 2** HLA-A, B, and C antigen frequencies (%) in each group

	Control group			Non-DR group			PDR group			Control v non-DR			Control v PDR			non-DR v PDR		
	n	%	(n, %)	n	%	(n, %)	n	%	(n, %)	$\chi^2$	p Value	Odds ratios	$\chi^2$	p Value	Odds ratios	$\chi^2$	p Value	Odds ratios
A1	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0.000	NS	—	—	NS	—	0.000	NS	—
A2	19	(38.0)	(18, 40.0)	18	(40.0)	(15, 34.1)	15	(34.1)	(15, 34.1)	0.040	NS	1.088	0.155	NS	0.844	0.155	NS	0.844
A11	10	(20.0)	(17,8)	8	(17.8)	(10, 22.2)	10	(22.2)	(10, 22.2)	0.076	NS	0.865	1.000	NS	0.471	0.338	NS	0.776
A24 (9)	29	(58.0)	(28, 62.2)	28	(62.2)	(29, 65.9)	29	(65.9)	(29, 65.9)	0.176	NS	1.193	0.620	NS	1.400	0.131	NS	1.360
A26 (10)	11	(22.0)	(10, 22.2)	10	(22.2)	(11, 25.0)	11	(25.0)	(11, 25.0)	0.001	NS	1.013	0.118	NS	1.182	0.095	NS	1.174
A28	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0.000	NS	—	—	NS	—	0.000	NS	—
A30 (19)	1	(2.0)	(0,0)	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0.910	NS	0.000	0.889	NS	0.000	0.000	NS	0.000
A31 (19)	10	(20.0)	(9, 20.0)	9	(20.0)	(8, 18.2)	8	(18.2)	(8, 18.2)	0.000	NS	1.000	0.264	NS	0.757	0.252	NS	0.757
A33 (19)	8	(16.0)	(7, 15.6)	7	(15.6)	(8, 18.2)	7	(15.9)	(7, 15.9)	0.101	NS	0.839	0.079	NS	1.167	0.109	NS	1.206
B7	5	(10.0)	(4, 8.9)	4	(8.9)	(5, 11.1)	4	(9.1)	(4, 9.1)	0.034	NS	0.878	0.022	NS	0.900	0.001	NS	1.025
B13	1	(2.0)	(1, 2.2)	1	(2.2)	(2, 4.4)	0	(0.0)	(0,0)	0.006	NS	1.114	0.889	NS	0.000	0.989	NS	0.000
B17	1	(2.0)	(1, 2.2)	2	(4.4)	(2, 4.4)	1	(2.3)	(1, 2.3)	0.463	NS	2.279	0.008	NS	1.140	0.322	NS	0.500
B27	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0.000	NS	—	—	NS	—	—	NS	—
B35	8	(16.0)	(7, 15.6)	9	(20.0)	(8, 18.2)	7	(15.9)	(7, 15.9)	0.258	NS	1.313	0.000	NS	0.993	0.252	NS	0.757
B37	1	(2.0)	(0,0)	0	(0.0)	(0,0)	4	(9.1)	(4, 9.1)	0.910	NS	0.000	2.337	NS	4.900	4.283	NS	—
B39	4	(8.0)	(3, 6.7)	3	(6.7)	(4, 9.1)	5	(11.4)	(5, 11.4)	0.062	NS	0.821	0.306	NS	1.474	0.600	NS	1.795
B40	1	(2.0)	(0,0)	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0.910	NS	0.000	0.889	NS	0.000	—	NS	—
B44 (12)	8	(16.0)	(7, 15.6)	10	(22.2)	(8, 18.2)	6	(13.6)	(6, 13.6)	0.597	NS	1.500	0.103	NS	0.829	1.112	NS	0.553
B46	5	(10.0)	(4, 8.9)	5	(11.1)	(5, 11.1)	2	(4.5)	(2, 4.5)	0.031	NS	1.125	1.010	NS	0.429	1.323	NS	0.381
B48	3	(6.0)	(2, 4.4)	2	(4.4)	(3, 6.7)	4	(9.1)	(4, 9.1)	0.115	NS	0.729	0.324	NS	1.567	0.764	NS	2.150
B51 (5)	9	(18.0)	(8, 17.8)	8	(17.8)	(9, 20.0)	6	(13.6)	(6, 13.6)	0.001	NS	0.985	0.332	NS	0.719	0.288	NS	0.730
B52 (5)	11	(22.0)	(10, 22.2)	10	(22.2)	(11, 25.0)	13	(29.5)	(13, 29.5)	0.001	NS	1.013	0.701	NS	1.487	0.623	NS	1.468
B54 (22)	9	(18.0)	(8, 17.8)	8	(17.8)	(9, 20.0)	6	(13.6)	(6, 13.6)	0.001	NS	0.985	0.332	NS	0.719	0.288	NS	0.730
B55 (22)	2	(4.0)	(2, 4.4)	1	(2.2)	(2, 4.4)	1	(2.3)	(1, 2.3)	0.245	NS	0.545	0.226	NS	0.558	0.000	NS	1.023
B56 (22)	2	(4.0)	(2, 4.4)	2	(4.4)	(2, 4.4)	0	(0.0)	(0,0)	0.012	NS	1.116	1.798	NS	0.000	2.001	NS	0.000
B59	2	(4.0)	(2, 4.4)	2	(4.4)	(2, 4.4)	6	(13.6)	(6, 13.6)	0.012	NS	1.116	2.791	NS	3.789	2.298	NS	3.395
B60 (40)	5	(10.0)	(4, 8.9)	3	(6.7)	(5, 11.1)	6	(13.6)	(6, 13.6)	0.341	NS	0.643	0.300	NS	1.421	1.189	NS	2.211
B61 (40)	12	(24.0)	(10, 22.2)	10	(22.2)	(12, 27.3)	14	(31.8)	(14, 31.8)	0.042	NS	0.905	0.715	NS	1.478	1.040	NS	1.633
B62 (15)	8	(16.0)	(7, 15.6)	8	(17.8)	(8, 18.2)	6	(13.6)	(6, 13.6)	0.053	NS	1.135	0.103	NS	0.829	0.288	NS	0.730
B67	1	(2.0)	(0,0)	1	(2.2)	(1, 2.3)	0	(0.0)	(0,0)	0.006	NS	1.114	0.889	NS	0.000	0.989	NS	0.000
B70	1	(2.0)	(0,0)	1	(2.2)	(1, 2.3)	0	(0.0)	(0,0)	0.006	NS	1.114	0.889	NS	0.000	0.989	NS	0.000
B75	1	(2.0)	(0,0)	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0.910	NS	0.000	0.889	NS	0.000	—	NS	—
Cw1	16	(32.0)	(12, 27.3)	12	(27.3)	(16, 36.4)	12	(27.3)	(12, 27.3)	0.324	NS	0.773	0.250	NS	0.797	0.004	NS	1.031
Cw3	23	(46.0)	(20, 44.4)	20	(44.4)	(23, 52.2)	22	(50.0)	(22, 50.0)	0.023	NS	0.939	0.150	NS	1.174	0.276	NS	1.250
Cw4	7	(14.0)	(6, 13.6)	14	(31.1)	(7, 15.6)	9	(20.5)	(9, 20.5)	4.027	0.045	2.774	0.690	NS	1.580	1.318	NS	0.569
Cw5	1	(2.0)	(0,0)	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0.910	NS	0.000	0.889	NS	0.000	—	NS	—
Cw6	1	(2.0)	(0,0)	1	(2.2)	(1, 2.3)	4	(9.1)	(4, 9.1)	0.006	NS	1.114	2.337	NS	4.900	1.979	NS	4.400
Cw7	11	(22.0)	(10, 22.2)	7	(15.6)	(11, 25.0)	7	(15.9)	(7, 15.9)	0.640	NS	0.653	0.561	NS	0.671	0.002	NS	1.027
Cw8	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0	(0.0)	(0,0)	0.000	NS	—	—	NS	—	—	NS	—
Cw9	6	(12.0)	(5, 11.1)	2	(4.4)	(3, 6.7)	1	(2.3)	(1, 2.3)	1.753	NS	0.341	3.213	NS	0.171	0.322	NS	0.500
Cw10	7	(14.0)	(6, 13.6)	2	(4.4)	(3, 6.7)	2	(4.5)	(2, 4.5)	2.522	NS	0.286	2.416	NS	0.293	0.001	NS	1.024

Numbers in parentheses are percentages. NS = not significant. All p values were not significant other than Cw4 with p = 0.045 in the control v non DR test.

**Table 3** HLA-DQ and -DR antigen frequencies (%) in each group

Control group	Non-DR group	Control v non-DR			Control v PDR			Non-DR v PDR				
		PDR group	$\chi^2$	p Value	Odds ratios	$\chi^2$	p Value	Odds ratios	$\chi^2$	p Value	Odds ratios	
DR1	4 (8.0)	3 (6.7)	4 (9.1)	0.062	NS	0.821	0.036	NS	1.150	0.180	NS	1.400
DR2	16 (32.0)	11 (24.4)	13 (29.5)	0.665	NS	0.688	0.066	NS	0.891	0.294	NS	1.296
DR3	0 (0.0)	0 (0.0)	0 (0.0)	—	NS	—	—	NS	—	—	NS	—
DR4	15 (30.0)	23 (51.1)	26 (59.1)	4.398	0.036	2.439	5.937	0.014	2.804	0.932	NS	1.510
DR6	14 (28.0)	8 (17.8)	6 (13.6)	1.391	NS	0.556	2.883	NS	0.406	0.288	NS	0.730
DR7	1 (2.0)	0 (0.0)	0 (0.0)	0.910	NS	0.000	0.889	NS	0.000	—	NS	—
DR8	11 (22.0)	7 (15.6)	7 (15.9)	0.640	NS	0.653	0.561	NS	0.671	0.002	NS	1.027
DR9	24 (48.0)	14 (31.1)	13 (29.5)	2.815	NS	0.489	3.340	NS	0.454	0.026	NS	0.928
DR10	1 (2.0)	0 (0.0)	0 (0.0)	0.910	NS	0.000	0.889	NS	0.000	—	NS	—
DR11	1 (2.0)	1 (2.2)	4 (9.1)	0.006	NS	1.114	2.337	NS	4.900	1.979	NS	4.400
DR12	2 (4.0)	1 (2.2)	0 (0.0)	0.245	NS	0.545	1.798	NS	0.000	0.989	NS	0.000
DR13	8 (16.0)	3 (6.7)	2 (4.5)	2.015	NS	0.375	3.230	NS	0.250	0.189	NS	0.667
DR14	6 (12.0)	4 (8.9)	3 (6.8)	0.243	NS	0.715	0.726	NS	0.537	0.132	NS	0.750
DRHR5	1 (2.0)	1 (2.2)	0 (0.0)	0.006	NS	1.114	0.889	NS	0.000	0.989	NS	0.000
DRHR6	3 (6.0)	2 (4.4)	1 (2.3)	0.115	NS	0.729	0.798	NS	0.364	0.322	NS	0.500
DR52	19 (38.0)	13 (28.9)	9 (20.5)	0.880	NS	0.663	3.445	NS	0.420	0.850	NS	0.633
DR53	33 (66.0)	29 (64.4)	31 (70.5)	0.025	NS	0.934	0.214	NS	1.228	0.366	NS	1.316
DQ1	32 (64.0)	28 (62.2)	20 (45.5)	0.032	NS	0.926	3.257	NS	0.469	2.518	NS	0.506
DQ2	1 (2.0)	0 (0.0)	0 (0.0)	0.910	NS	0.000	0.889	NS	0.000	—	NS	—
DQ3	28 (56.0)	23 (51.1)	15 (34.1)	0.228	NS	0.821	3.625	NS	0.449	1.965	NS	0.547
DQ4	17 (34.0)	12 (26.7)	20 (45.5)	0.601	NS	0.706	1.287	NS	1.618	3.410	NS	2.292
DQ6 (1)	6 (12.0)	8 (17.8)	13 (29.5)	0.629	NS	1.586	4.468	NS	3.075	1.709	NS	1.940
DQ7	6 (12.0)	1 (2.2)	4 (9.1)	3.317	NS	0.167	0.208	NS	0.733	1.979	NS	4.400

Numbers in parentheses are percentages. NS = not significant. All p values were not significant other than DR4 with p=0.036 in the control v non DR test and 0.014 in the control v PDR test.

p = 0.045) and DR4 ( $\chi^2 = 4.398$ , p = 0.036) than the control group (tables 2 and 3). While there was no significant difference between non-DR group and PDR group in any of the HLA antigens. The PDR group showed higher frequencies of HLA DR4 than the control group ( $\chi^2 = 5.937$ , p = 0.014).

**Comment**

Type 1 diabetes is aetiologically different from type 2 diabetes. Type 1 diabetes is caused by a failure in the autoimmune system, is clearly associated with specific HLA antigens.<sup>10</sup> Type 2 diabetes is not autoimmune and has less association or linkage with genes in the HLA region than type 1.

The type 2 diabetic patients in this study showed a typical HLA pattern. Other research has reported that DR3, DR4, and Cw4 increased in patients with type 2 diabetes mellitus.<sup>2-4</sup> These findings are consistent with our present results. Additionally an increase in HLA-DR4, which is in linkage disequilibrium with the DQB1\*0302 allele has previously been reported in patients with type 2 diabetes.<sup>2,3</sup> This increase was mainly reported to be restricted to patients with relative insulin deficiency or antibodies to islet cells or to glutamic acid decarboxylase.<sup>4</sup>

DR4 was detected in 59.1% of the PDR group, but this was not significantly different from the frequency in the non-DR group (51.1%). DR4 may, therefore, be related to the onset of type 2 diabetes, but not to the development of retinopathy. The HLA-DR4 levels reflected the antibody levels in the pancreatic Langerhans island but not the parameter of diabetic change in the retina.

In summary, our research suggests that HLA antigen investigations may be useful for predicting the prognosis of younger onset type 2 diabetes, but not for retinopathy in these patients. Finally, we must precisely

define the alleles or combination of alleles which cause increased susceptibility to PDR.

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**Effect of docosahexaenoic acid supplementation on retinal function in a patient with autosomal dominant Stargardt-like retinal dystrophy**

The gene, *ELOVL4*, is mutated in Stargardt-like macular dystrophy, a juvenile onset disorder. *ELOVL4* is homologous to a fatty acid elongase presumably involved in the biosynthesis of docosahexaenoic acid, DHA.<sup>1</sup>



Humans can synthesise DHA from precursors in small amounts, which may not be sufficient for normal retinal function if intake is minimal.<sup>2</sup>

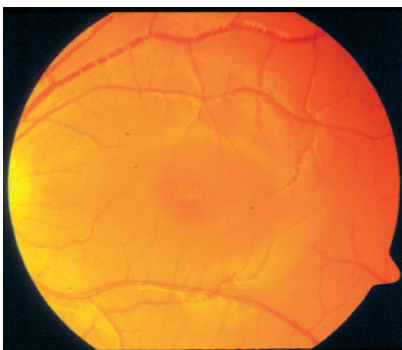
### Case report

A 15 year old girl with Stargardt-like macular dystrophy and a mutation in *ELOVL4* was given a dietary supplement of DHA on two occasions. A 7 day dietary history, prior to starting DHA supplementation, estimated her daily intake of DHA as 20 mg, in a diet of 1602 kcal. Beginning in April 2001, she was supplemented with 20 mg/kg body weight per day of DHA in capsules (Martek BioSciences, Columbia, MD, USA). Her functional response was determined by a VF-14 questionnaire,<sup>3</sup> visual acuity testing, multifocal electroretinography (mfERG), and plasma phospholipid analysis.<sup>4</sup>

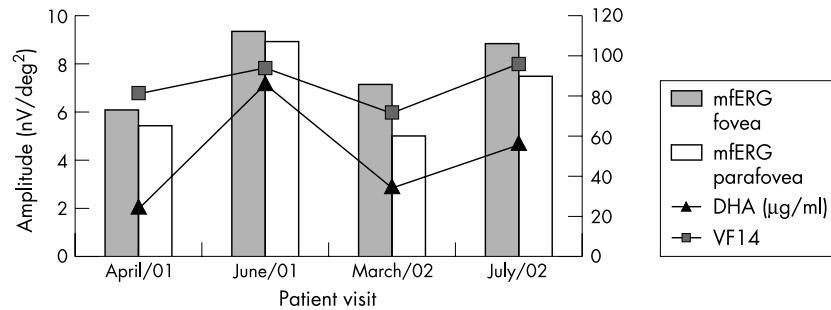
At baseline, fundus photography showed minimal macular changes (fig 1); however, the mfERG revealed significant macular dysfunction. A full field ERG performed in March 2000 revealed a reduction of approximately 30–40% in rod and cone responses, with the predominant effect on the b-wave amplitude in comparison with normative data (DTL electrode, dilated pupils, recorded according to ISCEV standards). No anomaly of latency was observed in either the mfERG or full field ERG recordings.

Peripheral blood samples were taken in a non-fasting state at the beginning of the study. Her baseline plasma DHA level was at the low end of the median for a North American diet, 24 µg/ml; whereas her omega-6 arachidonic acid was 76 µg/ml. Her plasma DHA level increased after 2 months of supplementation to 86 µg/ml (fig 2). She reported progressive subjective improvement in vision on the VF-14 questionnaire. Analysis of the mfERG tracings revealed that an improvement had occurred in amplitudes from the foveal and parafoveal regions of the macula (fig 2). For this study, we accepted the group average response of rings 1–2 (0–5°), and rings 3–5 (5–25°), derived from a 63 hexagon stimulus (Veris, San Mateo, CA, USA), as simulating the foveal and parafoveal responses respectively. Visual acuity improved from 20/200 to 20/100 only in her left eye with the DHA supplementation.

Unfortunately, she lost interest in the study, became non-compliant despite our encouragement, and was lost to follow up from August 2001 to the end of March 2002. She returned after perceiving that her vision had declined since halting the DHA supplementation. Repeat plasma DHA testing con-



**Figure 1** Fundus photograph of 15 year old patient at baseline examination.



**Figure 2** Effect of DHA on retinal function in patient with *ELOVL4* mutation.

firmed that her plasma DHA had dropped to levels approaching those from the beginning of the study (35 µg/ml, fig 2). Supplementation was once again initiated. After 4 months (July 2002), she showed the same improvements in visual function both subjectively (VF-14 score) and objectively (mfERG amplitudes, fig 2), coincident with an increase in plasma DHA.

The patient's visual acuity again improved only in the left eye from 20/200 to 20/100. Another full field ERG was conducted in July 2002 to compare with the diagnostic series from March 2000. The amplitudes of the photopic b-wave and the scotopic b-wave both improved by 30%, averaging both eyes. The scotopic mixed rod-cone response showed increased amplitude of the a-wave by 85%, and b-wave by 46%, when responses from both eyes were averaged. These results could not be explained by intervisit variability and suggest the effect of DHA supplementation occurs beyond the macula, over the entire retina.

### Comment

The patient's young age, low dietary intake of DHA, and a mutation in *ELOVL4* may have particularly predisposed her to an early macular degeneration. A longer experience with DHA supplementation in young patients with Stargardt-like macular dystrophy could determine if DHA supplementation can alter the natural history.

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### Severe retinopathy of prematurity (ROP) in a premature baby treated with sildenafil acetate (Viagra) for pulmonary hypertension

Sildenafil is used as a selective pulmonary vasodilator in children with primary pulmonary hypertension and severe lung fibrosis.<sup>1</sup> It improves gas exchange, increasing life expectancy and exercise tolerance. Recent animal models of neonatal pulmonary hypertension have also shown that sildenafil reduces vascular resistance. This has encouraged its use in units treating premature infants.<sup>2</sup> We report a case of severe retinopathy of prematurity in a preterm infant who was treated with intravenous sildenafil for severe respiratory failure.

### Case report

The patient was born at 26 weeks gestation weighing 525 g. He was ventilated from birth for respiratory insufficiency, secondary to respiratory distress syndrome. He required high flow oxygen ventilation and received surfactant at delivery and 16 hours later. His oxygen requirements then stabilised at 30–50%.

At 29 weeks his oxygen requirements increased to 100% due to coagulase negative *Staphylococcus aureus* and candida sepsis. He was treated with ampicillin and 5-flucytosine. However, he was only able to maintain oxygen saturations of 70–80% while receiving positive pressure ventilation on 80–90% oxy-

gen. At 31 weeks +2 days post-conception he was commenced on inhaled nitric oxide (NO) 5–40 ppm. There was no demonstrable improvement in oxygenation with the NO, and therefore it was decided to start sildenafil 3 days later in addition to the NO. During the period of treatment with sildenafil, there was an improvement in his clinical condition, with his oxygen requirements falling to 30–40% by 33 weeks. A subphrenic collection was discovered at 33 weeks, and ciprofloxacin and metronidazole were started. The sildenafil was discontinued at 34 weeks of life, after 16 days of treatment, because of a rising alanine aminotransferase level. There was no rebound hypoxia observed. Other than intrauterine growth retardation, no further risk factors for ROP such as intraventricular haemorrhage were identified.

The patient was examined by an ophthalmologist weekly from 31 weeks. No ROP was seen up to and including the 33 week check. At 34 weeks he was found to dilate poorly, to have bilateral iris neovascularisation, hazy media, and dilated and tortuous fundal vessels. Peripherally he had developed 7 contiguous clock hours of stage III ROP in zone II in the right eye, and 5 clock hours in the left. He was treated the following day with bilateral peripheral laser photocoagulation to ischaemic retina. The ROP regressed over the ensuing weeks and he remains under review.

**Comment**

Sildenafil relaxes arteriolar smooth muscle in the presence of nitric oxide by inhibiting phosphodiesterase type 5 (PDE5). PDE5 is found in high concentrations in the smooth muscle of the corpus cavernosum, and in lower concentrations in other tissues such as vascular smooth muscle. NO may control retinal blood flow. Measurement of ocular blood flow changes following sildenafil have shown conflicting results, with some groups showing a significant increase and others showing no increase in choroidal blood flow.<sup>3,4</sup>

In ROP, the initial constriction of retinal vessels by the high levels of oxygen induces a neovascular drive through the release of growth factors such as vascular endothelial growth factor. Subsequent retinal hyperperfusion has been linked to progression of other neovascular disease such as diabetic retinopathy,<sup>5</sup> by the local release of growth factors and free radical production. In addition, NO and cGMP accumulation caused by PDE5 inhibition has been proposed to exert a proliferative effect on retinal post-capillary venules.

Although sildenafil seems to have a unique place in the treatment of preterm infants in respiratory failure, this case may link its use to the development of aggressive ROP. We have observed a recent increase in treatable ROP in our unit, coinciding with the use of sildenafil. Further work on the retinal effects of sildenafil may be of use in determining whether it truly is a risk factor in the pathogenesis of ROP.

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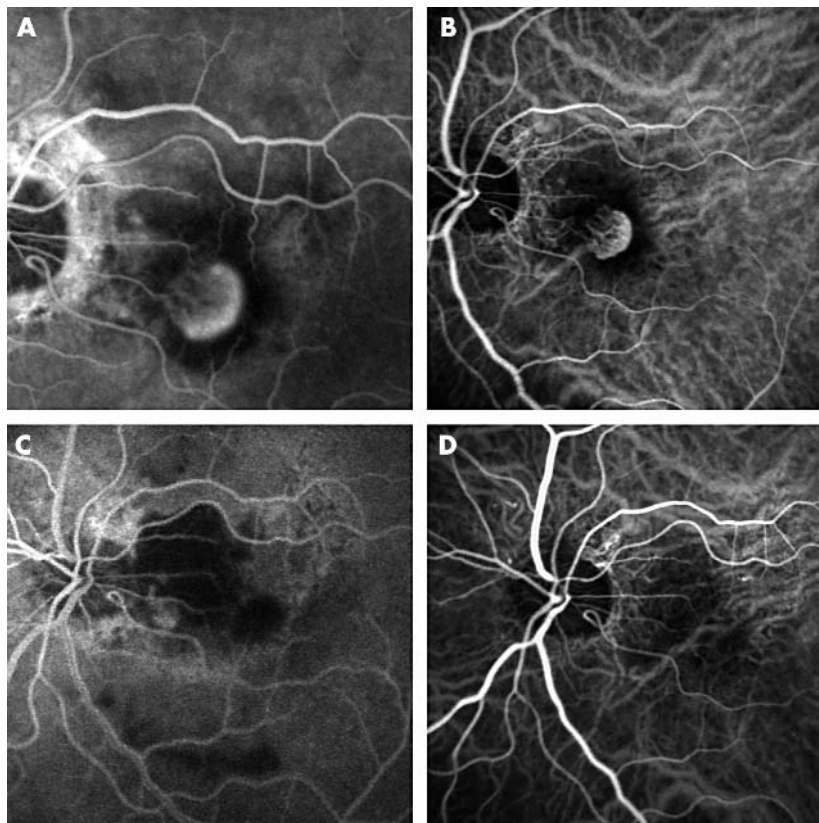
**Indocyanine green localisation in surgically excised choroidal neovascular membrane in age related macular degeneration**

Clinical indocyanine green (ICG) angiography has gained an established role in the diagnosis of choroidal neovascularisation (CNV) in age related macular degeneration (AMD).<sup>1,2</sup> It is potentially able to localise CNV with greater accuracy compared with fluor-

escien angiography because it fluoresces in the infrared range, allowing imaging of choroidal pathology through blood and pigment.<sup>3</sup> Additionally ICG angiography may better define CNV because of its high protein binding affinity in serum,<sup>4</sup> resulting in reduced leak from the CNV. This allows ICG angiography to clearly delineate the feeding vascular supply to the CNV allowing direct ablative thermal laser to precisely target this supply.<sup>5</sup>

Treatments for CNV, including thermal laser, photodynamic therapy, and macula translocation are all reliant on the ability of the clinician to diagnose accurately the location and nature of CNV. Few clinicopathological data exist to correlate the ICG angiographic appearance of CNV with its histology. The presence of CNV was shown pathologically in an eye with a plaque like hyperfluorescence on ICG angiography shown years previously.<sup>6</sup> Lafaut reported the pathology of surgically removed recurrent CNV in two eyes that were preoperatively imaged with ICG angiography.<sup>7</sup> The hyperfluorescence of drusen on ICG angiography in the monkey model has been correlated with ICG dye that has been found histologically on infrared fluorescence microscopy.<sup>8</sup>

In this case report we hope to correlate ICG angiographic findings in a patient with exudative AMD with the histological localisation of ICG to the surgically excised CNV. This will verify that ICG angiographic findings are an accurate representation of the location and nature of the CNV.



**Figure 1** Clinical angiography. (A) Preoperative fluorescein angiography shows that the lesion is well defined and extends into the fovea. (B) Preoperative mid-phase ICG angiogram shows the feeding vascular network that is originating from a peripapillary site. (C) Postoperative fluorescein angiography shows the removal of the CNV. (D) Postoperative ICG angiogram confirms the removal of the CNV.

## Case report

A 71 year old patient with classic subfoveal CNV was recruited into this study to histologically localise ICG dye to excised CNV in AMD. The study was granted institutional research approval by the Sydney Eye Hospital Ethics Committee.

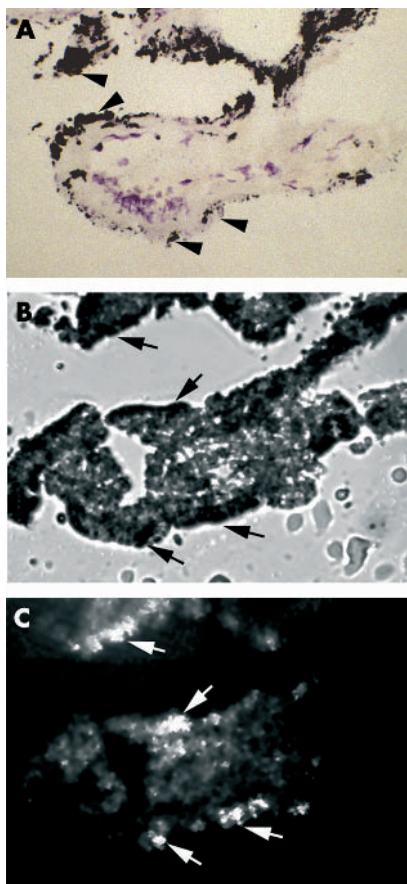
## Angiographic evaluation

The patient underwent preoperative imaging with fluorescein and ICG angiography to define the nature and location of the CNV. The angiographic studies were performed on the Heidelberg Scanning Laser Ophthalmoscope (Heidelberg, Germany). Diagnostic studies were performed using 5 ml of 10% fluorescein dye and 25 mg of ICG dye (Pulsion Medical Suppliers, München, Germany).

Follow up angiographic studies were performed one month following surgical removal of the new vessel using standardised methods as outlined above. This was done to confirm the removal of the new vessel.

## Surgical procedure

The patient underwent surgical removal of the CNV under assisted peribulbar regional anaesthesia 72 hours later. A three port trans



**Figure 2** Light and infrared fluorescence microscopy. (A) Light microscopy of excised CNV reveals patchy islands of intact RPE monolayer as indicated by the arrowheads. (B) Bright field image shows the surgical specimen after frozen sectioning. The arrows indicate intact RPE. (C) Infrared fluorescence microscopy demonstrating that ICG fluorescence is localised to the excised CNV. Areas of intact RPE cells are more intensely fluorescent.

pars plana vitrectomy and removal of the posterior vitreous hyaloid was performed. A small retinotomy adjacent to the CNV was made through which a localised retina detachment was created. The CNV was extracted with subretinal forceps through the retinotomy. Haemostasis was achieved by raising the height of the infusion bottle, increasing intraocular pressure. A fluid-air exchange was carried out after checking the retina periphery for tears.

## Histologic localisation of ICG dye

Fifteen minutes before excising the CNV, 50 mg of ICG dye was administered as an intravenous bolus to allow the ICG to bind to the CNV.

The excised specimen was taken immediately to be fixed in 20% dimethyl sulphoxide (Sigma, NSW, Australia) plus 80% adult fixative containing 2% paraformaldehyde in 0.1 M phosphate buffered saline (PBS) (pH 7.4) for 20 minutes.

The tissue was embedded in a small tissue embedding mold with Tissue-Tek OCT 4583 compound embedding medium (Bayer, NSW, Australia) and then rapidly frozen in liquid nitrogen. The frozen tissue block was mounted onto Cryostat Microtome (Leitz, Kryostat 1720, Australia) and 20  $\mu$ m sections were cut. Sections were collected with gelatin-chrom-Alum coated slides and air dried. Sections were then examined for ICG infrared fluorescence or stained with cresyl violet for histologic examination.

## Infrared fluorescence microscopy

The technique of infrared fluorescence microscopy to identify ICG fluorescence has been previously described.<sup>8</sup> An 810 nm diode laser (Iris Technologies) was used with an excitation filter to stimulate the surgical specimen. A Nikon Eclipse fluorescence microscope with a custom 860 nm barrier filter (Chroma Technologies, Vermont, USA) was used to detect the emitted ICG fluorescence. Paired bright field images with the corresponding infrared fluorescence image were used for orientation of the infrared fluorescence image and recorded digitally.

For histological studies, tissue sections were stained by cresyl violet for 30 seconds, rinsed and dehydrated in graded ethanol, cleared in xylene, and mounted in DePex (BDH, Melbourne, Australia). The sections were examined and photographed under light microscopy.

## Angiographic appearances

Fluorescein angiography shows a well defined hyperfluorescent lesion which extends under the fovea consistent with presumed CNV (Fig 1A). ICG angiography shows a hyperfluorescent vascular lesion in the same location (Fig 1B).

Postoperative fluorescein and ICG angiography (Fig 1C and D) reveal the absence of the hyperfluorescence confirming that the subfoveal lesion has been excised.

## Histologic localisation of ICG

Figure 2A shows the light microscopic image of the surgical specimen stained with cresyl violet. The CNV has a fibrovascular structure. There are associated patchy islands of intact retinal pigment epithelium (RPE) monolayer which are indicated by the arrowheads.

Figure 2B is a bright field microscopic image of the surgical specimen. Figure 2C is the corresponding fluorescence microscopic

image which shows ICG localised to the excised CNV. Note that the small islands of intact RPE cells indicated by arrows are intensely fluorescent.

## Comment

This report provides a direct clinicopathological correlation of CNV defined on ICG angiography, with ICG localised to the excised surgical membrane by infrared fluorescence microscopy. This is unique in that the ICG itself is detected within the excised CNV. This report confirms that hyperfluorescence defined on fluorescein and ICG angiography is consistent with CNV. The hyperfluorescent lesion shown preoperatively is absent following surgical removal of the specimen.

Indocyanine green was histologically localised to the fibrovascular structure of the CNV. It is proposed that ICG enters rapidly into the neovascular complex through its feeding vascular network. The ICG within the feeding vascular network is able to be imaged on the early phase clinical ICG angiography. Subsequently, it is likely that the ICG extravasates through the leaky vessels to bind to the supportive stromal tissues. In this later phase, clinical ICG angiography does not show the feeding vasculature.

Histologically, the CNV was associated with an incomplete layer of RPE cells which were removed with the CNV. This suggests that the CNV in the case studied appeared to be sub-RPE in location. This is consistent with the histopathology of specimens from the Submacular Surgery Trial which would indicate that the CNV in AMD tends to grow under the RPE.<sup>9</sup>

This report provides information regarding the interaction of ICG with RPE. The intact RPE that were removed with the CNV were intensely fluorescent on infrared fluorescence microscopy. The fluorescence of the RPE was more intense than the fibrovascular tissue. This suggests that that RPE cells accumulate ICG. This finding corroborates the previous histologic localisation studies in the monkey and human model which showed ICG localisation to the RPE.<sup>8</sup>

The frozen section technique was employed because it allows the water soluble ICG to remain within its in vivo location. Conventional histological processing would cause the ICG to leak through the tissue planes misrepresenting its true position. Previous histological localisation studies in the rat model have been performed using frozen section techniques.<sup>10</sup> Preservation of tissue architecture in this study was limited by crush artefact by the subretinal forceps and subsequent extraction from the subretinal space. Additionally, the frozen section processing technique results in tissue expansion and disruption.

This clinicopathological correlation provides the clinician with greater confidence in diagnosing CNV based on ICG angiography.

## Acknowledgement

The study was granted institutional research approval by the Sydney Eye Hospital Ethics Committee.

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## Correction of pseudophakic anisometropia in a patient with pseudoexfoliation using an implantable contact lens

Pseudophakic anisometropia may cause significant patient dissatisfaction with marked visual problems. Correction methods include contact lenses, intraocular lens (IOL) exchange, piggybacking a supplementary IOL, and corneal refractive surgery.

The Staar surgical implantable contact lens (ICL) was first used to correct myopia and hyperopia in phakic patients. It is now being used to correct pseudophakic anisometropia.<sup>1,2</sup>

The following case describes the successful management of pseudophakic anisometropia using an ICL in a patient with high myopia and pseudoexfoliation.

### Case report

An 80 year old woman was referred to us for correction of pseudophakic anisometropia. She had bilateral pseudoexfoliation and was highly myopic, her original refraction being

–14.00 DS right eye, –13.50/+1.75×20 left eye.

In 1989 she underwent left cataract extraction with posterior chamber IOL, keeping her highly myopic (–13.00/–2.00×105 left eye).

She subsequently developed cataract in her right eye so underwent uncomplicated right phacoemulsification with posterior chamber lens implantation, leaving her +1.00/–1.00×45 in her right eye.

Because of her marked anisometropia she experienced visual difficulties unresolved with spectacles or contact lenses, so she requested permanent correction of this.

Refraction, keratometry, corneal thickness (using pachymetry), axial length (using ultrasound), anterior chamber depth, and horizontal white to white diameter (using Orbscan), were measured and sent to Staar Surgical who calculated the ICL power.

A –19.0 Dioptre Staar Collamer ICL was inserted via an injector into the left sulcus, anterior to her posterior chamber IOL, through a corneal tunnel. Two iridotomies were made. Antibiotic and steroid drops were used postoperatively.

Postoperative refraction was right eye +1.00/–1.00×45 6/12, left eye +3.00/–1.00×105 6/12+2. Her symptoms resolved and she was extremely pleased.

### Comment

Insertion of a Staar Collamer ICL seems to be an effective alternative method for correcting anisometropia in pseudophakic patients.

All surgical options have their risks and complications.

Corneal refractive surgery is irreversible and complications include flap related problems, corneal scarring,<sup>3</sup> variable refractive outcome, and regression.<sup>2</sup>

Supplementary anterior chamber lenses risk corneal endothelial cell loss,<sup>4–6</sup> pupil abnormalities, and they need larger incision sizes. Posterior chamber IOLs can be used in “piggyback,”<sup>7</sup> but may risk interface opacities.

IOL exchange can be difficult, especially if performed some years after the original surgery where the capsular bag has shrunk around the IOL,<sup>1</sup> increasing the risk of capsular damage with subsequent vitreous loss, and zonule damage, especially important in patients with pseudoexfoliation whose zonules are already weak.

A main complication using ICLs is pupillary block glaucoma.<sup>8–10</sup> It can be avoided by performing adequate iridectomies preoperatively. Other side effects include glare, halos and lens decentration (minimised if accurate white to white diameter is measured in order to get an accurate fit).<sup>1</sup>

Advantages include ICL power calculation being based on actual refraction so repeat biometry is not required. There is no ICL/IOL touch because of vaulting of the ICL and so perhaps less risk of interface opacities.<sup>1,7</sup> The operation is minimally invasive with a small incision, as ICLs are thinner than other IOLs (60 µm) and more flexible. The small incision size (3 mm) reduces further astigmatism.

ICL power and diameter calculations made by Staar are devised for phakic eyes. No alterations were made for our pseudophakic patient. This may lead to error, though the six patients of Hsuan *et al*<sup>1</sup> had no major errors.

Our patient was slightly hyperopic, probably because of the different ciliary sulcus anatomy in pseudophakic patients, accentuated further by pseudoexfoliation.

It is better to prevent postoperative refractive surprises, but if they do occur, insertion of an ICL can be used to correct pseudophakic anisometropia, especially in patients with pseudoexfoliation.

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## Dopamine is an indicator but not an independent risk factor for grade 3 retinopathy of prematurity in extreme low birthweight infants

Retinopathy of prematurity (ROP) is a multifactorial disease with numerous risk factors.<sup>1</sup> Indicators besides birth weight or gestational age might be used to further discriminate the relative risk of developing ROP associated with a given gestational age or birth weight. Dopamine might be such an indicator since Mizoguchi *et al* reported on the association of dopamine and the risk of developing ROP in survivors (n = 41) with a birth weight below 1000 g and suggested that this association might be causal.<sup>2</sup>

To document whether dopamine is an indicator or an independent risk factor for developing ROP, a retrospective chart review in extreme low birthweight (ELBW—that is, below 1000 g) infants in a single neonatal intensive care unit during a 2 year period (2000–1) was performed. Neonatal characteristics collected were birth weight, gestational

age, and Apgar score. Respiratory characteristics were either markers of duration of respiratory disease (day at first extubation, last day of respiratory support, last day of supplemental oxygen) or markers of severity of respiratory disease in the first 72 hours of life: maximal mean airway pressure (MAP) and oxygenation index ( $\text{MAP} \times 100 \times \text{fractional oxygen/arterial oxygen mm Hg}$ ) at maximal MAP. In addition, data on CRIB (Clinical Risk Index for Babies, a disease severity scoring system) score were collected. The CRIB score was originally developed to document risk for neonatal mortality but there are reports on its association with morbidity characteristics.<sup>3,4</sup> Finally, prescription characteristics of dopamine (prescribed or not, maximal dose, and total hours of administration in the first week of life) were recorded.

Ophthalmological screening was initiated at the postnatal age of 4 weeks by indirect funduscopy after dilation. Screening was continued until full vascularisation or until diode laser therapy for threshold disease was provided. Findings were classified according to the International Classification of Retinopathy of Prematurity.<sup>5</sup> Clinical characteristics in infants who developed grade 3 ROP were compared with infants who did not (Mann-Whitney U or  $\chi^2$  tests). Characteristics of dopamine administration were entered in a multiple regression model (MedCalc) with other significant risk factors to document the potential independent effect of dopamine on the risk of developing grade 3 ROP.

Of 90 infants admitted with a birth weight below 1000 g, 69 survived until discharge.

Retinopathy (any grade) was documented in 45/69 (65%) survivors. Twenty seven (39%) survivors developed grade 3 ROP and 15 (22%) of these infants developed threshold ROP. In survivors ( $n = 69$ ), gestational age ( $p < 0.001$ ) and birth weight ( $p < 0.003$ ) were significantly lower in infants who developed grade 3 ROP while CRIB ( $p < 0.002$ ), oxygenation index ( $p < 0.02$ ) but not MAP were significantly higher in grade 3 ROP cases. All markers of duration of respiratory disease (ventilation ( $p < 0.02$ ), respiratory support ( $p < 0.001$ ), supplemental oxygen ( $p < 0.005$ )) were significantly higher in survivors who developed grade 3 ROP.

Forty seven (68%) survivors received dopamine. Incidence of any retinopathy, grade 3 ROP, and threshold ROP was higher in infants who received dopamine during the first week of life (table 1). Maximal dose ( $p < 0.05$ ) was significantly higher and duration (hours) ( $p < 0.03$ ) in the first week of life was significantly longer in infants who developed grade 3 ROP. When the strongest marker of cardiovascular instability—that is, duration (hours) of dopamine administration

in the first week of life was entered in a multiple regression model with either maximal oxygenation index or maximal MAP or CRIB score, dopamine was no longer an independent risk factor to develop threshold ROP.

### Comment

In line with Mizoguchi, an association of dopamine with an increased risk to develop ROP was found.<sup>2</sup> In addition, dopamine was no longer an independent risk factor of developing grade 3 ROP after correction for either CRIB score or oxygenation index in a multiple regression model.

Although it is hypothesised that a synergistic effect of hypoxia and dopamine might induce retinal vascular constriction in early neonatal life,<sup>2,6,7</sup> it is more likely that this risk factor is merely an indicator of cardiovascular instability and not an aetiological factor involved in the pathogenesis of ROP.

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## Consent of the blind and visually impaired: a time to change practice

It is a general legal and ethical principle that valid consent must be obtained before starting treatment or physical investigation of a patient. The validity of consent does not depend on the form in which it is given (verbal or written), rather it depends on it being given voluntarily by an appropriately informed person who has the capacity to consent to the intervention in question. Written consent merely serves as evidence of consent. There is no English statute setting out the general principles of consent, rather it is set by precedent or case law ("common law"). Hence, in visually impaired people (VIPs), instead of written consent should we not have moved to a better alternative—recorded audio consent (RAC)—legally equivalent as a record of consent but practically superior as a method? There are many good reasons why we should.

Firstly, health professionals are required to take all reasonable steps to facilitate communication with the patient, using interpreters or communication aids as appropriate.<sup>1</sup> The Department of Health has issued guidance on communication with patients who have sensory disabilities.<sup>2</sup> For those who cannot see, RAC would be more in line with these guidelines and recommendations than written consent.

Secondly, the problems with vision are frequently compounded by poor hand-eye coordination and manual dexterity especially as most VIPs (2.4 million in England and Wales) are over 65 years old.<sup>3</sup> RAC would overcome the problems in these circumstances. Further, as many procedures VIPs have are not eye related and the consenting practitioner non-eye trained (therefore not used to dealing with VIPs and their difficulties), non-ophthalmic units would also benefit from this technique.

Thirdly, we speak faster than we write and in any event the whole process needs to be undertaken verbally in the first instance. RAC would be a time saving exercise.

Fourthly, ever advancing current technologies allow for large volumes of audio recording in a more space efficient manner than cumbersome written consent. These devices (digital recorders, dictaphones, and others) are now available on the mass market at relatively low cost or already present within the health services.

Fifthly, section 21 of the Disability Discrimination Act<sup>4</sup> states that service providers are obliged to take reasonable steps to change practices, policies, or procedures which make it impossible or unreasonably difficult for a disabled person to use a service. As from 2004 steps will have to be taken to remove difficulties altogether. RAC works strongly in conjunction with this act.

Finally, a practitioner trying to convince an opposing party that a blind person had been able to read the form they signed, thus providing evidence of informed consent,

**Table 1** Dopamine use in survivors ( $n = 69$ ) and its association with the incidence and severity of retinopathy in extreme low birthweight infants ( $p$  value calculated using  $\chi^2$  test)

	Dopamine	No dopamine	p Value
Number	47	22	
No ROP	29%	45%	NS
Any ROP	70%	54%	NS
Grade 3 ROP	44%	27%	NS
Threshold ROP	30%	5%	<0.04

would certainly find it more difficult to prove than if the whole consent process had been recorded with RAC.

RAC would thus benefit patients and practitioners alike, facilitating consent and making it a more robust process in the United Kingdom and other countries alike.

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## Magnetic resonance angiography source images in carotid cavernous fistulas

Several investigations, including magnetic resonance imaging (MRI), computed tomography (CT), and orbital ultrasound are used to non-invasively screen for carotid cavernous fistula (CCF), with variable results. Examination of magnetic resonance angiography (MRA) source images, in addition to the conventional MRA reconstructions, is now also recognised as a useful method of detecting CCF.<sup>1</sup> The finding of a hyperintense signal in the cavernous sinus on MRA source imaging provides additional, and sometimes the only, neuroradiographic CCF evidence. We present this patient to familiarise the ophthalmologist with the typical CCF appearance on MRA source images.

## Case report

A 59 year old woman with a left eye pressure sensation and a four year history of left ear

pulse-synchronous "buzzing" was found to have elevated left intraocular pressure (26 mmHg) on routine examination. She denied diplopia, visual blurring, or pain. Visual acuity was 20/25 OD and 20/20 OS. Colour vision, visual fields, and pupils were normal. There was left proptosis, ptosis, and dilated episcleral vessels. Optic discs were normal and there was mild left retinal venous engorgement. There was a left supraorbital pulse-synchronous bruit. T1-weighted brain MRI showed left superior ophthalmic vein (SOV) enlargement (Fig 1). The cavernous sinuses were symmetric and normal in size, with slightly increased flow voids in the left cavernous sinus. Conventional reconstructed MRA did not reveal a fistula. However, MRA source images showed an enlarged, hyperintense left cavernous sinus (Fig 2), supporting the presence of a CCF. Cerebral angiography confirmed a left dural CCF. Following endovascular therapy with transvenous and transarterial embolisation of the fistula, all abnormal findings resolved.

## Discussion

Carotid cavernous fistulas are abnormal communications between the carotid artery and the cavernous sinus, either directly or via intradural branches of the internal or external carotid arteries.<sup>1</sup> Direct fistulas are high flow, frequently follow trauma, and tend to have a dramatic clinical presentation. In contrast, indirect fistulas are low flow, often spontaneous, and may have a subtle clinical presentation. Symptoms and signs common to both types of fistulas include proptosis, chemosis, diplopia, visual loss, pulse-synchronous tinnitus, orbital bruit, elevated intraocular pressure, dilated episcleral veins, and retinal venous congestion. The pattern of venous drainage, either anterior into the ophthalmic veins or posterior into the petrosal sinuses, often dictates the clinical findings and radiographic appearance. Anterior drainage typically leads to the most dramatic ocular findings and enlargement of the superior orbital vein, the latter often detectable with CT or MRI. However, superior orbital vein enlargement is not specific to

CCF.<sup>2</sup> Additional radiographic findings with variable prevalence include lateral bulging of the cavernous sinus wall and enlargement of extraocular muscles on CT or MRI, and abnormal cavernous sinus flow voids on MRI.<sup>3-5</sup> Conventional MRA reconstructed images rarely provide additional useful information. Direct visualisation of flow related hyperintensity on the source images of three dimensional time-of-flight MRA can be extremely helpful in CCF detection, with 83% sensitivity and 100% specificity, far superior to standard MRI.<sup>1</sup> Examination of MRA source images is particularly useful in the absence of anterior drainage and superior orbital vein enlargement. Gadolinium-enhanced MRA source images do not increase diagnostic accuracy.<sup>1</sup> In our patient, superior orbital vein enlargement and slightly increased flow voids in the region of the CCF were present on MRI, but MRA source images provided the most striking and direct evidence of CCF. Similar to other non-invasive techniques, MRA source images cannot delineate CCF arterial feeders or detect cortical venous drainage. Hence, conventional angiography remains necessary for definitive management. However, non-invasive techniques such as MRA source images have an important role in pre-angiographic diagnostic decisions.

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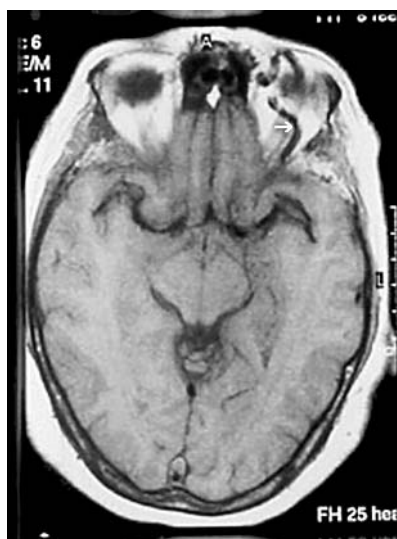


Figure 1 T1-weighted axial magnetic resonance image. There is dilation of the left superior ophthalmic vein (arrow).



Figure 2 Magnetic resonance angiography source image shows an enlarged, hyperintense left cavernous sinus (arrow).

## MAILBOX

### Response to allegations and some considerations on interferon treatment in Behçet's disease

Kotter *et al* refer to some problems, such as fabrication of authorship, possibly data, and ethical transgressions,<sup>1</sup> in our article published in the *Lancet*.<sup>2</sup> However, they do so without knowing the current facts about an ongoing process. They cite accusations that rely on an unfinished investigation from the year 2000. As we are now in 2003, I do feel that I have to present updated correct information.

Before I do that, however, I would like to note that the best scientific evidence against fabrication of the results is its reproducibility by other groups. The results of Kotter *et al*<sup>1</sup> show the beneficial effect of interferon in Behçet's disease just as our results did,<sup>2</sup> and our results are being increasingly reproduced.

The fact that the accusations were made on the basis of an unfinished investigation was clear in the editorial<sup>3</sup> and letter<sup>4</sup> written about our article at the time. The editor of the *Lancet* stated that "... further investigations are in progress"<sup>3</sup> and the Dean of our medical school stated that "... the issue will be finalised ... in a court of law."<sup>4</sup> I would like to report on the decisions made by courts of law during the 3 year period since then.

First of all, during ongoing inquiries about the article,<sup>2</sup> it was established without doubt by an investigating commission that all my coauthors had already known that their names were included as coauthors *before* the article was published. None of the coauthors had objected to the inclusion of his/her name at the time. It was not until 2 months after the publication that some of the coauthors claimed that they were unaware of inclusion of their names. It is noteworthy that they did so only *after* an ethical inquiry was embarked upon. The issue of fabricated authorship was brought to a court, accusing me of forging signatures. The court unambiguously declared my innocence at its first session on the matter on 3 April 2003, concluding that there was no forging of signatures and that it cannot be imagined that the coauthors had been unaware of the article given the totality of the circumstances surrounding the issue.<sup>5</sup> This conclusion is supported independently.<sup>6,7</sup> As attested by those court decisions, there is no fabrication of authorship.

I was also accused of possible fabrication of many of the patients.<sup>4</sup> However, in a declaratory action taken by another court, it was definitely established that all 135 patients mentioned in the *Lancet* article<sup>2</sup> were officially registered at the Hacettepe University Medical School.<sup>8</sup>

At the same time, the highest administrative court, the State Council of Turkey (Danistay) issued a stay order against any administrative act due to the claimed ethical transgressions,<sup>9</sup> in favour of me. This decision was further approved at a plenary session held at the State Council of Turkey with the participation of members from all administrative chambers of the court.<sup>10</sup>

Kotter *et al* are unintentionally perpetuating incorrect accusations about me in the *BJO*.<sup>1</sup> I am hoping the impropriety of those accusations is clear in light of all the independent court decisions I describe above. Judicial decisions should be respected by everyone who believes in upholding the supremacy of law. It is my natural right to

respond and the readers of the *BJO* deserve to be informed by updated correct information.

There is no indication that either authorship or the results reported in the *Lancet* article<sup>2</sup> were fabricated. Besides judicial decisions, the best scientific evidence that the data are not fabricated is their reproducibility by other groups, as I mentioned at the beginning. It is well shown in the literature that our results<sup>2</sup> are being increasingly reproduced, and I am happy to see that. In our clinic, we have been using interferon in Behçet's disease since the early 1990s and we are among the first groups to use it in this disease. We published our preliminary results previously.<sup>11,12</sup> The main problem in Behçet's disease is to prevent serious complications such as vascular thrombotic attacks, ocular involvement, and their recurrences.<sup>13</sup> Conventional drugs and corticosteroids have very little, if any, effect on the course of such complications. The first 2 years of the disease is the most critical period and the disease generally runs a more severe course in patients in whom the disease is diagnosed at an age less than 30.<sup>14-16</sup> I believe that as interferon use is increased, ocular complications of Behçet's disease will be minimised as well as extraocular manifestations. I suggest that the earlier we begin interferon, the better.

### ADDENDUM

In the action of annulment, until a final decision was reached, the highest administrative court, the State Council of Turkey (Danistay) had issued a stay order against any administrative act due to the claimed ethical transgression,<sup>9</sup> in favour of me, stating that "...the administrative act would result in damages which are difficult or impossible to compensate, and at the same time the act is clearly unlawful...". On 5 November 2003, the 12th Chamber of the State Council of Turkey arranged a trial (file no 2002/883), this time for a final decision. At the end of the session, the prosecutor of the State Council of Turkey read his opinion which agreed with the unlawfulness of the act and suggested cancellation of any administrative act, after which the court gave its final decision.

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### Are we overlooking the side effects of the drugs in our zeal to conquer ARMD?

First of all let me congratulate the authors for their work on exudative ARMD. But there are still some issues which need to be brought into account:

1. Some published studies show that even 4.0 mg of intravitreal triamcinolone has significant side effects in terms of increased IOP and more so for eyes which needed the second dose of the triamcinolone, with a few of them even needing a filtration surgery. In this particular study however 25mg of Triamcinolone has been used which may cause even more increased elevation of IOP. This issue is an important one as many of our ARMD patients have co-existing chronic open angle glaucoma with a compromised blood supply of the optic nerve head. With the intravitreal steroids induced rise in IOP, we may tilt the balance on the wrong side thereby taking their peripheral vision along with the central loss due to the ARMD.<sup>1,2,5</sup>

2. The effect of intravitreal steroids in the progression of cataract is not emphasized very much in various studies. If earlier cataract surgery in treated ARMD patients is required, this has theoretical implications in terms of ultraviolet light exposure – one of the environmental factors implicated in ARMD. If there is no long term benefit for preventing the progression of ARMD with the steroids then why should we increase the chances of cataract in these patients thereby rendering their retina more vulnerable to damage caused by the UV radiation?<sup>2</sup>

3. Various in vitro studies suggest that down-regulation of inflammatory markers and changes in the endothelial cell permeability are probably the modes of action of triamcinolone in exudative ARMD, but all these actions are probably only for the duration when the steroids are in high concentration in the vicinity. To maintain high concentrations triamcinolone should be injected repeatedly and probably that is the reason the improvement fades with time in many patients. Moreover none of the studies published so far have been long enough to actually give a fair idea about the long term

outcome. The longest duration for which the follow up has been done is 18 months.<sup>3,4</sup>

We need data from multicenter, placebo-controlled trials on a much larger population with long-term follow-up to establish the efficacy of the drug and assess possible side effects and complications. Until then we should probably reserve this therapy for those cases where there is recurrence after laser treatment.<sup>5</sup>

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## BOOK REVIEWS

### Genetics for Ophthalmologists: the Molecular Genetic Basis of Ophthalmic Disorders

Graeme Black. Pp 368; £25. London: Remedica, 2002. ISBN 190134620X

This is Remedica's latest addition to its *Genetics for.....* series. Ophthalmologists can now join cardiologists, dermatologists, haematologists, oncologists, orthopaedic surgeons, chest physicians and rheumatologists in having their very own "genetics bible." The fact is that no self respecting ophthalmologist, paediatrician, or clinical geneticist should be without a copy.

Imagine, you are in the clinic and the patient sitting in front of you has what looks like a macular dystrophy. The age of the patient and the family history helps to some extent with the diagnosis but you can't quite remember what associations you should be looking for or which genes may be involved. Should you be taking blood for DNA analysis or is genetic testing still part of the distant future in the NHS? You find a reason why your patient needs to leave the room—refraction, visual fields, colour vision ... anything will do—you reach for your handy "bible" and flick straight to page 88. There you find 20 useful pages on macular dystrophies with fabulous illustrations to impress your patient. No need to go home feeling inadequate and wishing you had listened more in your genetics lectures (if you were lucky enough to have them). You can counsel

your patient appropriately and feel great! Thanks to Graeme Black.

Genetics is on the television, on the internet, and in the outpatient clinic. Patients come armed with questions and are often very well informed about their condition.

As clinicians we have to keep abreast of the rapid changes that are occurring in genetics. Over the past 20 years there has been a revolution in molecular medicine.

Advances in laboratory techniques have enabled diagnoses and even predictions of disease inheritance that were previously only given as risk estimates. How and where does the ophthalmologist find this information without spending hours on the internet or pouring through journals? Black has provided the answer in his book *Genetics for Ophthalmologists*.

In the introduction there is a list of useful websites that provide up to date information on inherited eye disease. The preface covers common but controversial issues that arise in counselling, such as whether it is ethical to perform predictive testing in children before the age of consent. Then you come to the meat of the book ... Black has provided the reader with a comprehensive coverage of inherited eye diseases starting at the cornea and working back towards the optic nerve. The format of the book is easy to follow with lots of colour photographs and useful summaries of the clinical and diagnostic criteria for each condition. Information about inheritance patterns, penetrance, the effect of mutations and whether genetic screening is currently possible will be invaluable to those involved in counselling families. There is also a very helpful glossary at the back for those less used to genetic terminology.

This is the type of book that should be in every outpatient clinic consulting room with a spare copy in the departmental library. *Genetics for Ophthalmologists* will appeal to paediatricians, clinical geneticists, and all those with an interest in inherited eye disease. While updates and revisions will no doubt keep the author busy, the reader can sit back in the confidence that an extensive literature review has already been done allowing more time to be spent with the patient discussing the impact of this wealth of information.

**Amanda Churchill**

### Oculoplastic surgery: review 1

Brian Leatherbarrow. Pp 376; £150.00. London: Martin Dunitz, 2002. ISBN 1-85317-942-6

This is a wonderfully detailed book by an experienced oculoplastic and orbital surgeon. It is remarkable, as most mortal oculoplastic surgeons would have struggled over 10 years to write such a book, but Brian Leatherbarrow has succeeded in concentrating his encyclopaedic knowledge into a comprehensive tome in only two years. The result is a first class book, consisting of 26 chapters, 364 pages, and over 1200 original colour drawings, clinical photographs, and black and white diagrams.

The book is logically organised with an introductory chapter, which outlines basic principles and distils these into simple oculoplastic aphorisms. This leads nicely into

10 chapters on common oculoplastic conditions: the eyelid malpositions (ptosis, entropion, and ectropion), facial palsy, and periocular tumour management/reconstruction. The book then gradually develops the link between oculoplastics and orbital surgery with five chapters on trauma: of the eyelid, simple orbital fractures, zygomatic fractures, and more complex orbital fractures. Even if you are not going to perform this type of surgery, it is worthwhile having an idea of what is involved.

There are then three very sound chapters on orbital surgery; assessment and principles, the options for surgical approaches to the orbit and the management of thyroid eye disease. Again there is this effortless, but essential, link between orbit and eyelid, with thyroid eyelid retraction correctly being covered here.

The lacrimal surgery chapter is comprehensive and is well illustrated.

Interestingly, blepharoplasty and eyebrow ptosis are placed quite late in the book, which initially seemed a little unusual. In fact, it is sensible, as both of these require the surgeon to have a deeper knowledge of brow and orbit anatomy, not least to manage potential complications. The illustrations of brow anatomy and the various approaches to brow ptosis are fabulous, and include up to date endoscopic techniques.

The chapters on enucleation, exenteration, and socket work are very sound, as is the final chapter on autogenous grafts, which should be read frequently.

Who is this book aimed at? Perhaps not the beginner, though if I were starting out now I would find this book, particularly with its fresh colour drawings, extremely helpful and inspirational. It is definitely a must as a reference for difficult cases and is also very practical to dip into, particularly before doing an operation that perhaps the surgeon has not performed for a few weeks or months.

Every ophthalmologist interested in oculoplastic surgery should seriously consider obtaining a copy of this book. There are so many tips in it, each time I open it I learn something new, even something as simple as using a piece of Steri-drape to mark the template for a skin graft.

The pictures and text are precise, clear, and uncluttered. I could hardly find any errors, perhaps figure 1.35 A and B should have been reversed (publisher's error?) and I am not sure I entirely agree about starving patients for 24 hours after a lateral orbitotomy, but I'll think about it.

I look forward to future editions.

**Jane Olver**

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### Oculoplastic Surgery: review 2

A useful new text had been added to the compendium of the oculoplastics library with the publication of this volume. The author's intent, as stated in the preface, was to provide a pragmatic approach to diagnosis and management of patients with a myriad of oculoplastic, orbital, and lacrimal conditions. This book accomplishes the goal of broadly covering many salient topics within the field of oculoplastics.

The author divides the book into sections on oculoplastic operative principles, eyelids, orbit issues including fractures, orbital disorders, and surgical approaches to the orbit.



The extensive coverage of orbital and mid-facial fractures is particularly comprehensive. A thorough review of thyroid ophthalmology is organised separately and provides a comprehensive approach to the many issues surrounding this disease process. Epiphora, blepharoplasty, eyebrow ptosis, enucleation, evisceration, exenteration, socket reconstruction are also covered in separate sections which contain many photographs and illustrations. Complications of various surgical procedures add to the topics, but are not ubiquitously covered in equal detail in all of the sections. A section on autogenous grafts in ophthalmic plastic surgery is well presented, and of interest in that infectious concerns are causing a return to popularity of autogenous grafts.

Many surgical photographs are accompanied by adjacent photographs of skulls nicely showing anatomy, or endoscopic photographs, which are also very illustrative. Less useful are the accompanying line drawings, many of which do not greatly clarify their accompanying surgical photographs, which are taken from some distance. At the end of each section is a reference for further reading, which would lead the reader to more in-depth information about the topics and surgical techniques discussed.

Although this book is very thorough in covering functional oculoplastics, it does not concentrate on the many cosmetic issues in oculoplastics. Botox, use of filler material, fat repositioning, laser resurfacing, and use of the carbon dioxide laser in surgery are not covered in this text.

Overall, this is a well thought out and nicely presented basic text on functional oculoplastics. It would complement the knowledge of residents, fellows, and the general ophthalmologist. Those beyond this level of training might find they want for more depth of information than this text offers.

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## CORRECTION

In the article by Michaelides *et al* in the November issue (*Br J Ophthalmol* 2003;87:1317–20) the legend to table 1 contained an error. The legend to table 1 on p 1319 should have read "ERG = electroretinography; CF = counting fingers; M-R = Mollon-Reffin test". It should not have read "ERG = counting fingers; M-R = Mollon-Reffin test". The journal apologises for the error.

## NOTICES

### HIV/AIDS and the eye

The latest issue of *Community Eye Health* (No 47) discusses the impact of the HIV/AIDS epidemic on prevention of blindness programmes. 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; website: www.jceh.co.uk). Annual subscription (4 issues) UK£28/US\$45. Free to developing country applicants.

### Second sight

Second Sight, a UK based charity whose aims are to eliminate the backlog of cataract blind in India by the year 2020 and to establish strong links between Indian and British ophthalmologists, is regularly sending volunteer surgeons to India. Details can be found at the charity's website (www.secondsight.org.uk) or by contacting Dr Lucy Mathen (lucymathen@yahoo.com).

### Specific Eye ConditionS (SPECS)

Specific Eye ConditionS (SPECS) is a not for profit organisation which acts as an umbrella organisation for support groups of any conditions or syndrome with an integral eye disorder. SPECS represents over 50 different organisations related to eye disorders ranging from conditions that are relatively common to very rare syndromes. The website acts as a portal giving direct access to support groups' own websites. The SPECS web page is a valuable resource for professionals and may also be of interest to people with a visual impairment or who are blind. For further details about SPECS, contact: Kay Parkinson, SPECS Development Officer (tel: +44 (0)1803 524238; email: k@eyeconditions.org.uk; website: www.eyeconditions.org.uk).

### The British Retinitis Pigmentosa Society

The British Retinitis Pigmentosa Society (BRPS) was formed in 1975 to bring together people with retinitis pigmentosa and their families. The principle aims of BRPS are to raise funds to support the programme of medical research into an eventual cure for this hereditary disease, and through the BRPS welfare service, help members and their families cope with the everyday concerns caused by retinitis pigmentosa. Part of the welfare service is the telephone help line (+44 (0)1280 860 363) for any queries relating to retinitis pigmentosa, especially for those recently diagnosed with retinitis pigmentosa (tel: +44 (0)1280 821 334; email: lynda@brps.demon.co.uk; website: www.brps.demon.co.uk).

### Surgical Eye Expeditions International

Volunteer ophthalmologists in active surgical practice are needed to participate in short term, sight restoring eye surgery clinics around the world. Contact: Harry S Brown, Surgical Eye Expeditions International, 27 East De La Guerra, C-2, Santa Barbara, CA 93101-9858, USA (tel: +805 963 3303; fax: +805 965 3564; email: hsbrown.md@cox.net or seeintl@seeintl.org; website: www.seeintl.org).

### Rise in organ transplant numbers

According to UK Transplant, the UK has seen the highest number of organ transplants in six years. Last year (1 April 2002 to 31 March 2003), 2777 patients had their lives saved or dramatically improved through the generosity of 1064 donors. This equated to a 6% increase compared to the previous 12 months (1 April 2001 to 31 March 2002). Furthermore, during 2002–3, the highest number of people benefited from a cornea transplant for five years (1997–98) and 240 more people had

their sight restored than the previous year. For further information see UK Transplant's website (www.uktransplant.org.uk).

### 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.

### 5th International Symposium on Ocular Pharmacology and Therapeutics (ISOPT)

The 5th International Symposium on Ocular Pharmacology and Therapeutics (ISOPT) will take place 11–14 March 2004, in Monte Carlo, Monaco. Please visit our website for details of the scientific programme, registration, and accommodation. To receive a copy of the Call for Abstracts and registration brochure, please submit your full mailing details to <http://www.kenes.com/isopt/interest.htm>. Further details: ISOPT Secretariat (website: [www.kenes.com/isopt](http://www.kenes.com/isopt)).

### XVth Meeting of the International Neuro-Ophthalmology Society

The XVth Meeting of the International Neuro-Ophthalmology Society will take place 18–22 July 2004, in Geneva, Switzerland. Further details: Prof. A Safran, University Hospital Geneva, c/o SYMPORG SA, Geneva (fax: +4122 839 8484; email: [info@symporg.ch](mailto:info@symporg.ch); website: [www.symporg.ch](http://www.symporg.ch)).

### 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](mailto:autoim04@kenes.com); website: [www.kenes.com/autoim2004](http://www.kenes.com/autoim2004)).

### 14th Meeting of the EASD Eye Complication study group

The 14th Meeting of the EASD Eye Complication (EASDEC) study group will take place on the 21–23 May 2004. There will be key lecture notes on the following topics: Peter Gaede (Denmark)—Results of the Steno 2 study, Hans Peter Hammes (Germany)—Animal models of diabetic retinopathy,

Massimo Porta (Italy)—Screening with the London protocols: 12 years after, and Anselm Kampik (Germany)—Surgical options in diabetic retinopathy. There will also be case presentations and oral and poster presentations. The EASDEC board comprises F Bandello (President), PJ Guillausseau (Vice President), C-D Agardh (Past President), P Massin (Secretary), M Porta (Treasurer). The Scientific and Organizing Committee includes: F Bandello, PJ Guillausseau, P Massin, C-D Agardh, M Porta, A Kampik, M Ulbig, and G Lang. There are three travel grants available, at 1000 Euro each, for young scientists (less than 35 years at the time of the meeting). Application for the grant should be made together with the submission of the abstract. For further information, contact: Department of Ophthalmology, Ingrid Mannl, Ludwig-Maximilians-University, Mathildenstr. 8, 80336 MUNICH, Germany (tel: +49-89-5160-3800; fax: +49-89-5160-4778; e-mail: easdec@ak-i.med.uni-muenchen.de. The deadline for abstracts is 2 March 2004.

### **A revolution in healthcare diagnostics**

A simple but revolutionary new design for an ophthalmoscope, that can be easily used to detect serious diseases of the eye, including glaucoma, diabetes and cerebral malaria, has won the NESTA (the National Endowment for Science, Technology and the Arts) prize at the 2003 Medical Futures Innovation Awards.

Mr Roger Armour, an Honorary Consultant Surgeon from Hitchin in Hertfordshire, will receive £10,000 in prize money and his idea will be fast tracked through NESTA's Invention & Innovation programme, the largest source of early stage seed funding in the UK, for possible further funding of up to £100,000 to take the technology to the next stage of development.

Ophthalmoscopes are used by physicians to examine the retina at the back of the eye. It is a powerful and useful clinical skill that is completely painless for the patient but essential in diagnosing diseases such as glaucoma and cataracts as well as a host of unsuspected diseases of other parts of the body affecting the eye. These include: high blood pressure, diabetes, leukaemia, brain tumours, hardening of the carotid arteries, cerebral malaria and the tragic shaken baby syndrome, which may be revealed to the trained observer.

With 30 lenses to manipulate and a dozen settings, current ophthalmoscopes are complicated to use, expensive and difficult to carry. As a result, most medical students cannot afford to buy them and many doctors never learn how to use this potentially life-saving instrument properly.

Roger's simple new design can be made significantly cheaper than standard ophthalmoscopes using basic materials and weighs only 30g so is easy to carry in a pocket or purse. It provides a service as good as current instruments but has no complicated settings or lenses to trouble the user.

It has also been successfully tried by over 300 doctors, nurses and non-medical people and won an award at the 2003 Oxford Ophthalmological Congress. NESTA Chairman Chris Powell, who presented the award, said:

"Roger's idea is a wonderful example of a simple innovation that could make a huge impact and I am delighted to present him with the NESTA award at this year's Medical Futures. His ophthalmoscope could revolutionise education and training in medicine, giving students an inexpensive and easy to use tool that they can carry everywhere with them. This will give them the chance to practice and perfect their technique in this essential skill without having to be confined to a clinic and could benefit doctors and patients for years to come."

### **International Strabismological Association (ISA) Fellowship**

The International Strabismological Association (ISA) has established one fellowship for either basic or advanced training in strabismus/paediatric ophthalmology supported by the amount of US \$10,000. Applications may be obtained from the Secretary/Treasurer or the ISA, Derek T. Sprunger, MD, at Indiana University School of Medicine, 702 Rotary Circle, Indianapolis, Indiana 46202 or by e-mail at isa.lms@juno.com. The last day for this application is 15 March, 2004.