

## LETTERS TO THE EDITOR

### Late dehiscence of healed corneal scars

EDITOR,—The stroma comprises about 90% of the total corneal thickness<sup>1</sup> and is responsible for most of the corneal tensile strength. Presumably because of its avascularity, healing of corneal stromal wounds is slower than in other connective tissues. Continued histopathological changes in human corneal laceration wounds have been observed years after injury, despite meticulous original suture closure.<sup>2</sup> The wounds appear to undergo perpetual, dynamic remoulding, a fine balance between constructive and destructive processes. We report three cases of late, full thickness corneal wound dehiscence occurring spontaneously or after minor blunt trauma 17–56 years after the original injury.

#### CASE REPORTS

##### Case 1

A 61 year old man was referred for spontaneous corneal perforation right eye. At age 5, he had sustained a full thickness corneal laceration in this eye which was repaired with sutures. The patient did well with an uncorrected visual acuity of 20/50 right eye until the time of his corneal perforation 56 years later, whereupon he noted the sudden onset of eye pain and loss of vision in this eye upon awakening 2 days before referral. He denied any recent eye trauma or antecedent vigorous rubbing of the eye. He was in excellent health with no previous history of corneal melting disorders. At the time of his first visit to us, the best corrected visual acuities were light perception right eye and 20/20 left eye. There was an inferonasal, 3 mm linear, vertically oriented corneal scar in the right eye not involving the limbus. The iris was incarcerated and externalised along an inferior 1.0 mm long dehiscence in the corneal scar, dragging the entire pupil into the perforation. The Seidel test showed a slow, spontaneous leakage of aqueous humour from the dehiscence. An emergency lamellar corneal patch graft was performed with excision of the dehiscence corneal scar and the prolapsed iris. Subsequent surgeries included pupilloplasty, cataract extraction, excision of cyclitic membranes, and penetrating keratoplasty. Pathological specimens revealed extensive epithelial downgrowth. The eye eventually became phthisical. Rheumatoid factor (RF), antinuclear antibodies (ANA), antinuclear cytoplasmic antibodies (ANCA), erythrocyte sedimentation rate (ESR), complete blood counts (CBC), and chemical profile were all normal.

##### Case 2

This 42 year old woman sustained a full thickness, 8 mm long, corneal laceration in the left eye at age 25 from an exploding glass bottle. The linear laceration was repaired with multiple 10-0 nylon sutures. During a routine follow up visit 17 years after the injury, the patient was able to see 20/60 without correction and 20/30 with a contact lens in the left eye. The corneal scar appeared well healed and stable. Three months later, she bumped her left eye on the edge of a door, after which

she noted mild soreness and a very slow decrease in vision in the left eye. Considering the mildness of the impact, she did not seek medical attention until her vision became noticeably worse. She presented to our clinic 2 weeks after the injury with a visual acuity of 20/20 right eye and counting fingers in the left eye. A self sealing, 5 mm, linear dehiscence of the corneal scar was found to be incarcerated with iris. The Seidel test was positive only upon provocation. The incarcerated iris was surgically released and the dehiscence corneal scar was repaired with 10-0 nylon sutures. Two weeks after surgery, the uncorrected visual acuity improved to 20/200 left eye. The RF, ANA, ANCA, ESR, CBC, and chemical profile were normal.

##### Case 3

While using an electric saw, a 68 year old man sustained a perforating wood chip injury of the cornea in his right eye. The resulting peripheral corneal laceration was repaired with 10-0 nylon sutures. A month later, the patient underwent elective extraction of a traumatic cataract in this eye. Subsequently, the best corrected visual acuity was 20/40 with a hard contact lens and spectacle overrefraction. Seventeen years after the injury, the corneal scar dehiscence spontaneously in the absence of recent trauma. A peripheral tectonic penetrating keratoplasty was performed, completely excising the dehiscence corneal scar. The patient later underwent a central, 8.0 mm, optical penetrating keratoplasty, combined with implantation of a posterior chamber intraocular lens by sulcus fixation. This resulted in a best corrected visual acuity of 20/20 in this eye.

#### COMMENT

These three cases illustrate the innate structural weakness of healed corneal scars. Two of the scars dehiscence without any mechanical provocation. Although corneal scars become optically dense and hypercellular, they never regain the full original preinjury tensile strength.<sup>3</sup> Unsutured wounds, such as radial keratotomy incisions, are particularly weak.<sup>4</sup> Even sutured full thickness wounds may not regain more than 50–70% of their original corneal tensile strength.<sup>3</sup> In penetrating keratoplasty, rupture after blunt trauma may occur many years after surgery and always occurs at the graft host junction, the weakest point in the cornea.<sup>5</sup> In full thickness corneal wounds, the discontinuity in Descemet's membrane further deprives the cornea of another important source of structural strength. Ancillary factors which may further reduce wound integrity include diabetes mellitus, poor suturing technique, incarceration of uvea or vitreous, and entrapment of epithelium.

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Accepted for publication 15 March 1999

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### Transpupillary thermotherapy of choroidal melanoma with or without brachytherapy: a dilemma

EDITOR,—Transpupillary thermotherapy (TTT) is a new approach to the treatment of choroidal melanoma with heat. The early treatment results seem favourable with regard to local tumour control and retained visual acuity; no early metastasis was found.<sup>1–3</sup> The reported rate of complications is low.<sup>2,3</sup>

The heat treatment is performed with a temperature calculated at 45–65°C, induced by an infrared diode laser (810 nm) with a large beam diameter (3 mm) and a long exposure time of 1 minute per application. These factors promote a deep penetration of heat into the choroidal melanoma. The result is tumour necrosis up to 3.9 mm deep and occlusion of blood vessels in the treated area as shown on histopathology.<sup>4</sup> Depending on the pigmentation of the tumour, the energy is raised or lowered stepwise until the desired effect occurs. The tumour is treated by overlapping applications extending beyond the margin of the tumour. The exposure time should not be shortened to less than 1 minute, as it takes 40 seconds to reach a temperature at subcoagulation level.

TTT is performed as an outpatient procedure and can be easily repeated. Treatment results can be evaluated in several ways. The outcome is favourable when the choroidal melanoma develops into a scar on ophthalmoscopic examination, substantial regression of the tumour thickness is seen on ultrasonography together with an increased reflectivity on the diagnostic A-scan, and hypofluorescence is visible in the treated area on the early and late phases of the fluorescein angiogram. TTT is not indicated in melanoma patients with severe media opacities, in patients with insufficient dilatation of the pupil, or in elevated, peripherally located melanomas.<sup>1</sup>

Simultaneous use of TTT with brachytherapy in the management of melanomas is called “sandwich therapy”, where the effect of TTT is maximal at the top of the tumour and brachytherapy efficiently treats the base of the tumour.<sup>1,2,4</sup> Combining both treatments has several advantages. It enabled us to treat patients with tumours thicker than 5 mm, generally the maximum height for ruthenium-106 brachytherapy.<sup>1,2</sup> Insufficient melanoma regression and/or recurrences after a combined treatment might be retreated with TTT alone. The combination might also lead to a decreased radiation dose of the isotope used in brachytherapy.

In principle, TTT can also be applied as the sole therapy. A satisfactory local tumour control is reported in the early years after TTT as sole therapy for small choroidal melanomas.<sup>3</sup> TTT as sole therapy seems especially attractive in treating small choroidal melanomas in and around the posterior pole. Visual outcome may be better after TTT than after brachytherapy because the laser beam, but not the radiation beam delivered by the radioactive plaque, can be focused.<sup>3</sup> As the macular capillaries are very radiosensitive to brachytherapy, this may finally result in radiation

maculopathy with a considerable loss of central vision. However, after extramacular applications of sole TTT, macular complications such as transient cystoid macular oedema may be also seen.<sup>3</sup> A dense scotoma is generally produced by TTT at the time of application, whereas a scotoma after brachytherapy usually does not develop for up to a year or several years. If heat treatment is performed as sole therapy, effective treatment of the sclera over the tumour is as important as treatment of the tumour itself because intra- and episcleral tumour invasion is present in, respectively, 55.7% and 8.2% of patients with medium and large tumours.<sup>5</sup> In a group of 21 patients with enucleated small melanomas, 17 showed scleral ingrowth on histopathological examination.<sup>6</sup> Intrasceral melanoma cells surviving treatment might be a focus for tumour recurrence, which is associated with a two to threefold higher risk of metastasis. This is evident from the results after photocoagulation treatment of choroidal melanomas showing a high rate of tumour regrowth. This might be attributed to the low depth of photocoagulation penetration, insufficient to destroy the intrasceral melanoma cells.<sup>7</sup>

In TTT as sole therapy, the question arises as to whether the effect of the heat induced by TTT to the choroidal melanoma is identical to the effect of the heat to the possible melanoma cells in the sclera. In one eye, intentionally enucleated after experimental TTT, total tumour necrosis up to the sclera was visible on histopathological examination. Despite heat damage to the inner layers of the sclera which was evident from scleral oedema and necrosis of sclerocytes, a cluster of tumour cells with a viable aspect was located near the inner border of the sclera.<sup>4</sup> A recent clinicopathological report on two cases of recurrent juxtapapillary choroidal melanoma after TTT revealed tumour cells appearing histopathologically intact and presumably viable.<sup>8</sup> One patient was insufficiently treated with TTT because of cataract, another patient was treated with TTT and brachytherapy. Interpreting these data, we have to keep in mind that a pathologist is often unable to guess viability of melanoma cells in an enucleated eye after any treatment, especially in an undertreated eye.

Unfortunately, no sensitive clinical techniques evaluate the effect of TTT on intra- and episcleral tumour cells, their destruction, and the early development of extrascleral recurrences. To reduce the risk of insufficient treatment of the sclera and because episcleral tumour recurrences rarely develop as a late complication of brachytherapy, one may consider combining TTT with brachytherapy (the sandwich therapy).

TTT remains an investigative procedure until long term results are available. In the meantime we have to choose between TTT as sole or combined treatment for patients with choroidal melanoma.

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Accepted for publication 12 March 1999

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#### Asymmetric diabetic retinopathy associated with Fuchs' heterochromic cyclitis

EDITOR.—Diabetic retinopathy (DR), with its complications, is the leading cause of blindness among the working population in developed countries. Asymmetric diabetic retinopathy (DR) has been defined as proliferative disease in one eye and background or no retinopathy in the fellow eye, persisting for at least 2 years.<sup>1</sup> Previous reports have described systemic and local factors associated with the development of asymmetric disease.<sup>1-2</sup> These include unilateral carotid artery stenosis, chorioretinal scarring, complete posterior vitreous detachment, amblyopia, unilateral elevated intraocular pressure, optic atrophy, retinal pigment epithelial atrophy, myopia  $\geq 5D$ , anisometropia  $>1D$ , concurrent retinal vascular disease, cataract extraction, vitreous loss, trauma, radiation, tumour, and unilateral recurrent panuveitis.

We observed a patient with proliferative DR in the right eye and no proliferative changes in the left eye which had Fuchs' heterochromic cyclitis (FHC). In the absence of other known risk or protective factors, FHC was felt to have protected against the development of proliferative DR. The significance of this new observation and the possible mechanisms are discussed.

#### CASE REPORT

The patient was a 56 year old insulin treated type II diabetic. He also had systemic hypertension and was a smoker. FHC of the left eye was diagnosed on the basis of typical stellate keratic precipitates scattered over the entire corneal endothelium, chronic low grade anterior uveitis, iris heterochromia, and posterior subcapsular cataract. Pharmacological testing with 4% cocaine excluded a diagnosis of Horner's syndrome in the left eye.

He suffered widespread vascular complications of his combined diabetic and hypertensive state, including nephrotic syndrome and peripheral vascular disease culminating in left below knee amputation. These were accompanied by the development of new vessels at the disc in the right eye (Fig 1A), but only background changes in the left eye, although

ischaemic changes were evident on fundus fluorescein angiography (Fig 1B).

At his initial assessment in the ophthalmology clinic, best corrected Snellen visual acuities were right eye 6/6; left eye 6/9. The refractive errors were right eye +1.00/+0.50@180; left eye +2.00 DS. Intraocular pressures were 16 mm Hg either eye. Retinal pigment epithelial changes were present at the left macula (Fig 1B) but there was no extensive retinal pigment epithelial atrophy or chorioretinal scarring. There was neither proliferative diabetic retinopathy nor clinically significant macular oedema in either eye.

Nine months after the first examination he developed clinically significant macular oedema in the right eye. This was treated with focal argon laser with resolution of the macular oedema. Two years later new vessels at the right disc (Fig 1A) were noted and panretinal photocoagulation was performed (2707 burns in two sessions). Despite laser treatment, vitreous haemorrhage ensued. Further laser treatment to the right eye (1149 burns) led to regression of new vessels at the right disc (Fig 2A). Cataract progressed in the eye with FHC so that 5 years after his first visit to the ophthalmology department left phacoemulsification with heparin coated intraocular lens implant was required. Extracapsular cataract extraction is associated with accelerated retinopathy progression postoperatively.<sup>3</sup> Accelerated retinopathy was defined as the development of any of the following within 6 months postoperatively: new clinically significant macular oedema, recurrent clinically significant macular oedema in eyes that had preoperative resolution of macular oedema after focal laser treatment, increased hard exudates or intraretinal haemorrhages in eyes

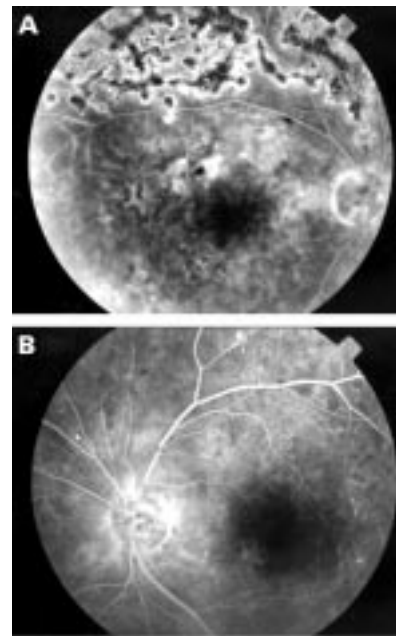
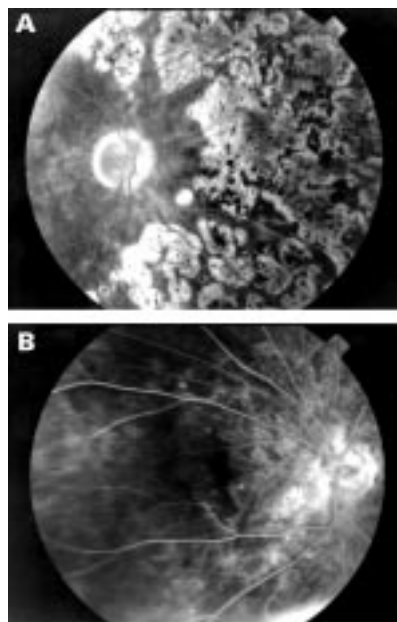


Figure 1 June 1996: fundus fluorescein angiogram. (A) Right eye, late venous phase. There is ischaemia of the superotemporal retina of the right eye. Superior panretinal laser scars and disc leakage from residual new vessels can be seen. (B) Left eye, mid venous phase. The left eye also shows some areas of capillary non-perfusion. There is hyperfluorescence at the superior aspect of the left disc but no characteristic leakage features of proliferative diabetic retinopathy. Note the small window defect inferonasal to the left fovea from an area of retinal pigment epithelial atrophy.



**Figure 2** April 1998; fundus fluorescein angiogram. (A) Right eye, late phase. After multiple sessions of panretinal laser the right eye shows regression of disc neovessels with no residual leakage. (B) Left eye, mid venous phase. Following cataract surgery the hyperfluorescence at the superior aspect of the left disc is unchanged. Worsening ischaemia of the nasal retina is evident but is not accompanied by progression to proliferative diabetic retinopathy.

with clinically significant macular oedema at the baseline examination, or new onset proliferative diabetic retinopathy. No such progression occurred in this patient. Six months after left phacoemulsification with intraocular lens implantation there was no clinically significant macular oedema and best corrected visual acuity was 6/6. Despite evidence of worsening retinal ischaemia there was no progression to proliferative diabetic retinopathy (Fig 2B).

He was investigated for any evidence of local or systemic factors which may have contributed to the asymmetric retinopathy. There was no anisometropia. Intraocular pressures were equal in both eyes. There was no posterior vitreous detachment in either eye, no optic atrophy, and visual fields were full. Ultrasound of the carotids excluded haemodynamically significant stenosis. Retinal macrocirculation and microcirculation were assessed by fundus fluorescein angiography. Arm-retina times were right eye 11.1 seconds; left eye 11.0 seconds (normal 10.9 (SD 2.6) seconds).<sup>4</sup>

#### COMMENT

Kohner *et al* have put forward a working hypothesis for the pathogenesis of DR.<sup>5-6</sup> The first change is hyperperfusion initiated by hyperglycaemia and influenced by high blood pressure and impaired autoregulation. The hyperglycaemia damages both pericytes and endothelial cells. The increased blood flow results in further damage to vessel walls, occlusion of some vessels, hypoxia, and ischaemia, resulting in proliferative DR. Factors which reduce or normalise retinal blood flow therefore have a protective effect in DR.

Although the aetiology of FHC is unknown, a vascular pathogenesis is one of the proposed hypotheses for its cause. An immune complex vasculitis may be the cause of abnormal hyalinisation of the iris vessel walls previously

described.<sup>7</sup> Ultimately there is narrowing of the vessel lumen, or even occlusion. This may explain the rubeosis and neovascular glaucoma sometimes seen in eyes with FHC.

Sympathetic theories for FHC have also been proposed, although a sympathetic aetiology has never been proved.<sup>8</sup> Loewenfeld and Thompson<sup>9</sup> felt there was inadequate evidence to support the proposed connection with sympathetic paralysis or denervation. Despite the arguments put forward in their review to reject the association between FHC and hemifacial atrophy (Parry-Romberg syndrome), and the hypothesis of a sympathetic defect implicated in both diseases, many authors still support this theory.<sup>10</sup> Sympathicoparalysis explains the increased permeability of the blood-ocular barrier, with escape of cell elements, primarily albumin and lymphocytes, into the aqueous<sup>7</sup> and vitreous. If denervation hypersensitivity occurs, because of an increase in receptor sites following destruction of postganglionic neurons, there may be rebound vasoconstriction with reduction in blood flow.

The arm-retina time measured by fluorescein angiography is a measure of the vascular system supplying the eye. The absence of any haemodynamically significant carotid artery stenosis and the normal arm-retina time suggest that there were no haemodynamic factors, even in the more distal branches of the internal carotid system, which contributed to the asymmetric retinopathy. In fact, pulsatile ocular blood flow in the left eye was normal (1101  $\mu$ l/min), despite signs of ischaemia on fluorescein angiogram (Fig 2B). Ocular blood flow in the right eye was also normal (824  $\mu$ l/min), although this was after extensive panretinal photocoagulation.<sup>6</sup> Our hypothesis, therefore, is that FHC protected his left eye from progression to proliferative diabetic retinopathy.

This case suggests that FHC protected against proliferative DR but the mechanism is unclear and merits further consideration. Hopefully, this new observation will help to increase our understanding of these complex diseases and eventually affect the formulation of clinical practice.

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Accepted for publication 9 March 1999

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#### Anterior capsular phimosis following AcrySof lens insertion

**EDITOR**,—Anterior capsular phimosis is one of the complications of continuous curvilinear capsulorhexis (CCC). It was first described by Hansen and the term "capsule contraction syndrome" was coined by Davison in 1993.<sup>1,2</sup> Capsular contraction has previously been reported to occur with poly(methylmethacrylate) (PMMA) and with silicone intraocular lenses (IOLs), particularly plate haptic silicone IOLs.<sup>3,4</sup> Several authors have reported that the anterior lens capsule is more stable when in contact with an acrylic IOL (AcrySof) compared with PMMA and silicone lenses.<sup>5-8</sup> To our knowledge this is the first case report of anterior capsular contraction following implantation of an AcrySof IOL.

#### CASE REPORT

A 77 year old white woman underwent uncomplicated phacoemulsification with insertion of a foldable acrylic (AcrySof, Alcon Laboratories, Hemel Hempstead) IOL (23.0 dioptre, 6.0 mm optical diameter, model number MA60BM) through a superiorly sited scleral tunnel (June 1998). The capsulorhexis diameter was between 5.0 and 5.5 mm. No attempt was made to remove anterior lens epithelial cells (LECs) during irrigation aspiration of lens cortex. Ophthalmic history was negative for uveitis, pseudoexfoliation, and myopia. Postoperatively she made a good recovery, achieving an unaided visual acuity of 6/9. Three months later she presented again because of reduced vision (6/24 corrected). Dilated examination revealed fibrosis as well as marked phimosis of the anterior capsular opening (Fig 1A). The contraction was symmetrical and no decentration or tilting of the lens was noted. There was no posterior capsular opacification of note. Nd:YAG radial anterior capsulotomy (193.5 mJ TE) was carried out (Fig 1B). She regained a visual acuity of 6/9 when reviewed 1 month later (Fig 1C).

#### COMMENT

The advent of CCC has led to the presentation of specific complications of this technique. These are capsule contraction syndrome, capsular bag distension, and LEC migration and proliferation onto the posterior capsule. It is now well recognised that capsule contraction syndrome is due to proliferation of residual anterior LECs that leads to fibrous metaplasia and eventual reduction of the capsular opening. Electron microscopy studies have revealed these to be cells resembling fibrocytes surrounded by a dense collagen matrix.<sup>9</sup>

Vision can be impaired not only because of opacification of the media but also because of tilting, decentration, and buckling (foldable only) of the IOL. In severe cases the zonular traction may lead to IOL dislocation and retinal detachment.<sup>2</sup> Anterior capsular shrinkage occurs more rapidly in the first 6 weeks postoperatively but continues slowly thereafter.<sup>4</sup>

Sickenberg *et al* have claimed that the stronger centrifugal force of the AcrySof IOL's

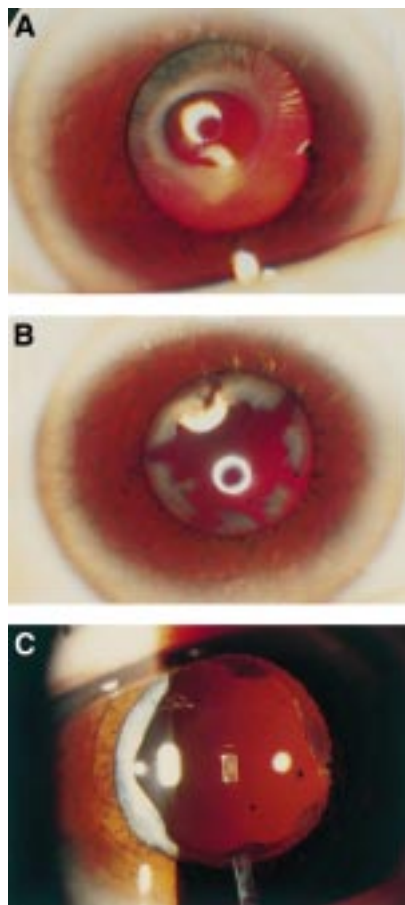


Figure 1 (A) Slit lamp photograph showing anterior capsular phimosis and fibrosis. (B) Appearance of anterior capsule immediately after Nd:YAG radial anterior capsulotomy. (C) Appearance of anterior capsule 5 weeks after laser.

haptics confer a greater stability to the anterior capsule compared with other foldable IOLs.<sup>6</sup>

Ursell and co-authors have analysed anterior capsular stability in AcrySof IOLs, and found this to be greater in contrast with PMMA and silicone IOLs.<sup>7</sup> In nearly all cases, the anterior capsular opening enlarged with time, probably because large capsulorhexes were made for extracapsular cataract surgery. The implant designs were similar so the authors argued that this difference was due to the difference in biomaterials. An interesting in vitro study on the adhesiveness of collagen to AcrySof lenses by Nagata *et al* hypothesised that the anterior capsule adheres more strongly to the IOL optic thus preventing LECs from undergoing fibrous metaplasia.<sup>8</sup>

We do not know why this rare complication should have occurred in our patient, but it may be that the capsulorhexis opening was too small for this particular lens capsular bag zonular apparatus complex. In any case, clinicians should be alerted by our case which shows that anterior capsular phimosis can occur with AcrySof lenses. The risk of anterior capsular phimosis may be increased with smaller capsulorhexis diameter independently of IOL biomaterial.<sup>10</sup>

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Accepted for publication 15 March 1999

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### Central serous retinopathy complicated by massive bilateral subretinal haemorrhage

EDITOR,—Central serous retinopathy (CSR) is a common cause of visual disturbance in the younger age group. Spontaneous visual recovery occurs in the majority of patients. A minority of patients, however, suffer permanent visual loss commonly caused by chronic retinal pigment epithelial changes. We report a devastating complication of untreated CSR, with bilateral massive subretinal and vitreous haemorrhages.

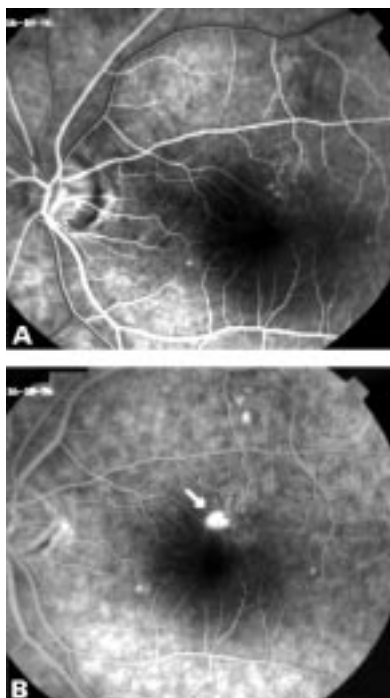


Figure 1 Fluorescein angiography of the left eye reveals pinpoint hyperfluorescence superior to the fovea (A) which shows progressive leakage in the later phase (arrow) (B), confirming the diagnosis of central serous retinopathy.

### CASE REPORT

A 43 year old Asian man presented with a 3 week history of blurred central vision and metamorphopsia affecting his left eye. Ocular examination revealed best corrected visual acuity of 6/9 in both eyes. Funduscopy revealed a neurosensory retinal detachment overlying the left fovea, with bilateral multiple retinal pigment epithelial changes. Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) confirmed the diagnosis of bilateral CSR (Figs 1 and 2).

The neurosensory retinal detachment in the left eye resolved spontaneously. Seven months after his initial presentation, he developed sudden loss of vision in his left eye to counting fingers at 1 metre. Ocular examination revealed a large macular subretinal haemorrhage, which progressed to a dense vitreous haemorrhage after a week. Ultrasonography revealed no evidence of a retinal detachment. The vitreous haemorrhage subsequently cleared spontaneously leaving an atrophic macular scar.

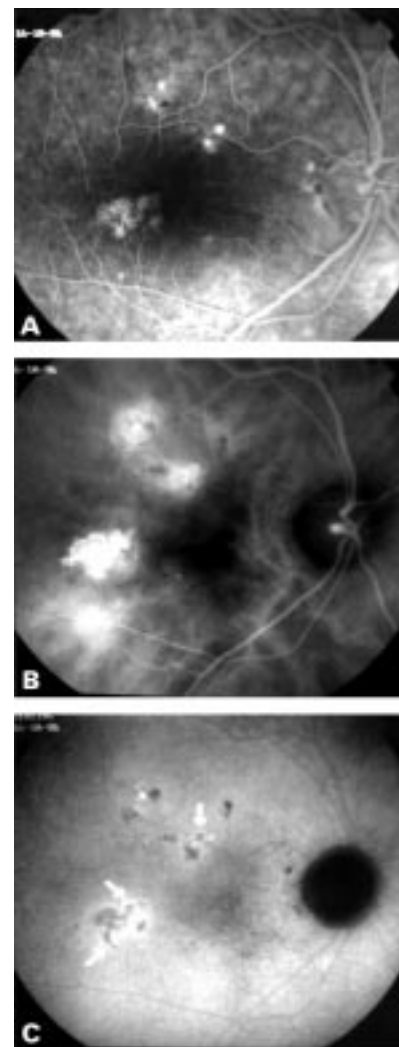
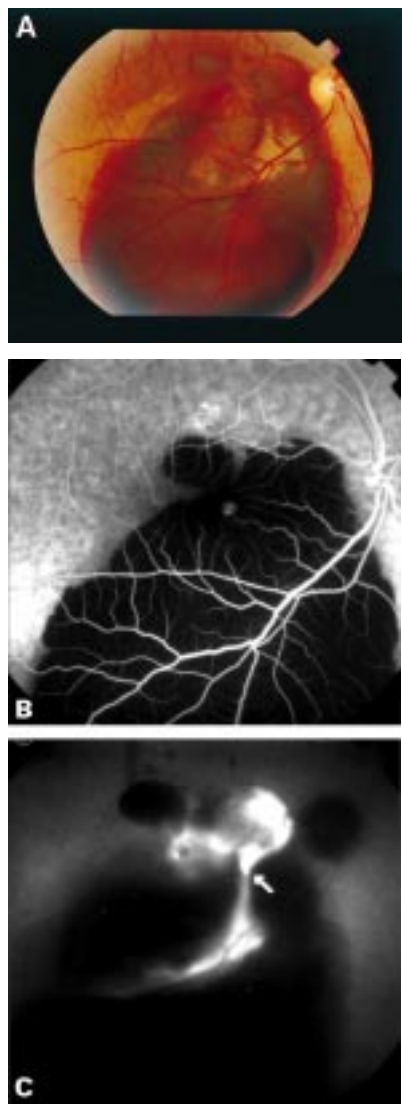


Figure 2 (A) Fluorescein angiography of the right macula reveals multiple areas of leakage; (B) ICGA reveals more extensive disease with diffuse hyperfluorescence representing multiple areas of choroidal hyperpermeability; (C) late phase ICGA demonstrates serous retinal pigment epithelial detachments with characteristic central hypofluorescence and hyperfluorescent staining of the surrounding ring (arrows).



**Figure 3** (A) Colour fundus photograph of the right eye shows extensive macular haemorrhages. Blood is present beneath the retinal pigment epithelium and the neurosensory retinal detachment. (B) Fluorescein angiography shows masking corresponding to the extensive haemorrhage. There is a small focal area of hyperfluorescence within the haemorrhage which has not changed its size or intensity throughout the angiogram. (C) ICGA reveals a large haemorrhagic retinal pigment epithelial detachment. A focal hyperfluorescent spot (arrow) represents a mechanical disruption (a hole) of the retinal pigment epithelium and ICG streams through the defect into the subretinal layer, forming a blood level as seen in the colour fundus photograph.

Eighteen months later, he again presented with a sudden loss of vision in his right eye. Best corrected visual acuity was 6/24 in the right eye and counting fingers in the left eye. Funduscopy confirmed a massive macular subretinal haemorrhage in the right eye. Fluorescein angiography showed extensive masking. ICGA demonstrated the presence of a haemorrhagic retinal pigment epithelial detachment (Fig 3). His visual acuity in the right eye returned to 6/12 after 3 months. Physical examination and investigations revealed no evidence of underlying systemic disease. Full blood count and coagulation screen were normal.

#### COMMENT

Massive subretinal macular haemorrhage can occur secondary to a number of causes such as choroidal neovascularisation (CNV), retinal artery macroaneurysm, idiopathic polypoidal choroidal vasculopathy, blood dyscrasia, or trauma. Histopathological analysis of patients with age related CNV, complicated by massive subretinal haemorrhage may be associated with rupture of a large choroidal blood vessel.<sup>1</sup>

CNV is known to occur infrequently in patients with CSR treated with laser photocoagulation.<sup>2</sup> In only two previous cases has CNV developed spontaneously in patients with CSR.<sup>3</sup> Massive subretinal haemorrhage, however, was not the feature in these two reported cases. In our case, the use of ICGA had helped to understand the mechanical events (Figs 2 and 3) but the underlying aetiology remains unclear.

The pathogenesis of CSR has been disputed. Recent studies with ICG suggest focal choroidal hyperpermeability as the possible initial event, leading to the formation of serous retinal pigment epithelial detachment. Excessive fluid accumulation then leads to pressure on the retinal pigment epithelium, resulting in either mechanical disruption or retinal pigment epithelial decompensation.<sup>4</sup> The chronic secondary retinal pigment epithelial changes, if extensive, could predispose to the development of CNV. In our patient, the sudden onset of haemorrhage in both eyes may in part be explained by the presence of disorganised and dysfunctional choroidal blood vessels. The latter leads to an initial increase in choroidal hyperpermeability (hence the CSR) and later, the tendency to rupture suddenly resulting in massive haemorrhage (as illustrated by our case).

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Accepted for publication 17 March 1999

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#### Various phenotypic expressions of familial aniridia with a *PAX6* mutation

**EDITOR.**—Aniridia is an uncommon congenital bilateral panocular disorder characterised by complete or partial absence of the iris and foveal hypoplasia. Aniridia can appear in a high penetrance form associated with other ocular anomalies such as keratopathy, foveal hypoplasia, cataract, ectopia lentis, and glaucoma.<sup>1</sup> Recent studies showed that aniridia is caused by mutation of the *PAX6* gene,<sup>2-4</sup> which controls early events in cerebral and ocular formation.<sup>4-7</sup> We present a pedigree with

various clinical findings of aniridia in which a mutation of the *PAX6* gene was identified.

#### CASE REPORTS

The family tree is shown in Figure 1A. Case I-1 is a 52 year old man with visual impairment and nystagmus. He had cataract from an early age (the detail was unknown). His vision was right eye finger counting at 20 cm and left eye 0.01; eye examination revealed bilateral partial aniridia, dense cataract, corneal pannus, and foveal hypoplasia (Fig 2A, B). His cataracts were removed and posterior chamber intraocular lenses were implanted at age 52. One son, II-1, is 16 years old with nystagmus, visual acuities of right eye 0.3 and left eye 0.2, bilateral corneal pannus, iris thinning, and mild foveal hypoplasia; his lenses were clear (Fig 2 C, D). Another son, II-2, is 14 years old with nystagmus, visual acuities of right eye 0.2 and left eye 0.2, bilateral iris thinning, corneal pannus, and mild foveal hypoplasia; his lenses were clear (Fig 2 E, F). Case II-3 is a 13 year old male with nystagmus, visual acuities of right eye 0.3 and left eye 0.2, corneal pannus, partial aniridia, zonular cataracts, and foveal hypoplasia (Fig 2 G, H). All affected patients were normal in size for age and had normal intelligence and karyotype (46XY). We analysed genomic DNA isolated from leucocytes of patients and family members. Genomic DNA representing 14 exons for the *PAX6* gene was amplified by polymerase chain reaction (PCR) and subjected to SSCP analyses.<sup>8</sup> An abnormal pattern for exon 11 was identified indicating a heterozygous mutation in all affected patients but not in unaffected members of the immediate family or in over 100 normal individuals (Fig 1A) Sequencing analysis demonstrated a deletion of a single nucleotide at the 1434th position (in this study, the numbers of the nucleotide and amino acid were based on the sequence of GenBank Accession No M93650) (Fig 1B). No other changes in nucleotide sequence were detected.

#### COMMENT

The human *PAX6* gene is 422 amino acids long and has paired box and homeobox DNA binding domains. These are separated by a 78 amino acid linker segment and followed by a 152 amino acid C-terminal region rich in proline, serine, and threonine (PST domain). In our cases, the *PAX6* mutation is predicted to result in amino acid substitutions from the 339th position and a truncation at the 344th position, resulting in a truncated protein product that ultimately excludes part of the PST domain. Truncated proteins generally tend to be degraded, thus haploinsufficiency of *PAX6* was believed to cause aniridia phenotype. However, biochemical assay recently indicated that truncation mutations in the PST transactivation region of *PAX6* result in dominant negative mutants.<sup>9</sup> A truncated protein of nearly normal size may function for a short time.

The affected individuals in this family had a wide variation of phenotypes, including thinning and the absence of the iris, various features of cataract, and foveal hypoplasia. Hittner *et al*<sup>10 11</sup> described suspected familial aniridia cases in which expressivity was variable as was seen in our cases. Probably many modifiers affect a variety of phenotypic expression in a pedigree with the same *PAX6* mutation. Because the *PAX6* gene is a master control gene,<sup>12</sup> it may control numerous downstream genes, whose expression pattern probably is slightly different among each individual. Af-

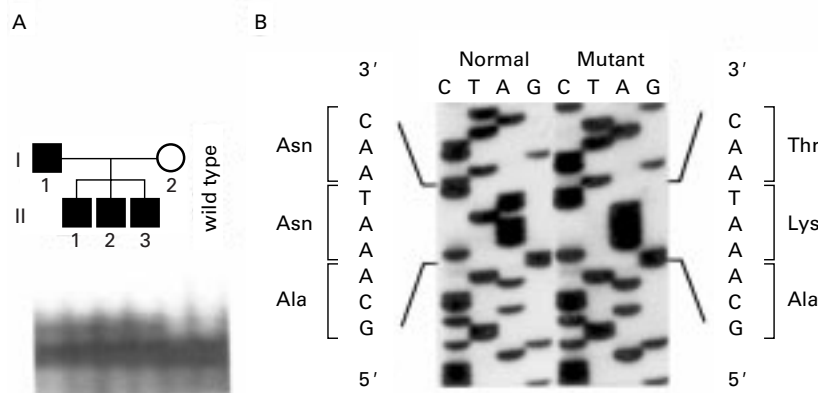


Figure 1 (A) PCR-SSCP analysis of exon 11 reveals a band shift in patients I-1, II-1, II-2, and II-3. (B) Sequencing of the normal and mutant alleles of I-1 identifies a single base deletion at nucleotide 1434 that causes a translational frameshift in the proline, serine, and threonine (PST) domain. Other affected members had the same mutation.

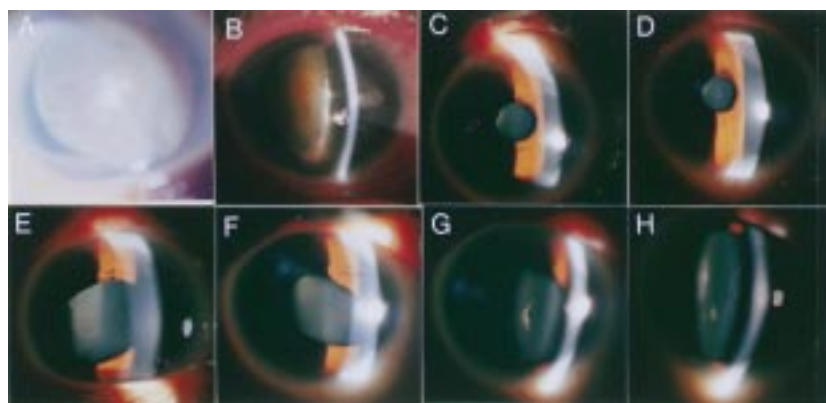


Figure 2 Photograph of anterior segment of case I-1 (A, right eye; B, left eye) with corneal pannus, absent iris, dense cataract; case II-1 (C, right eye; D, left eye) with corneal pannus and iris thinning; case II-2 (E, right eye; F, left eye) with corneal pannus, partially absent iris; and case II-3 (G, right eye; H, left eye) with corneal pannus, partially absent iris, and suture cataract.

affected patients may also reflect modifiers unlinked to the *PAX6* gene cascade, stochastic effects, or environmental factors. The fact that there was little difference in the phenotypes between two eyes of each individual in a pedigree also supports this hypothesis.

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Accepted for publication 22 March 2009

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#### Iopidine allergy causing lower eyelid entropion progressing to cicatricial entropion

EDITOR,—Apraclonidine hydrochloride 1% (Iopidine) is a selective  $\alpha_2$ -adrenergic agonist used to treat glaucoma or to protect against pressure spikes before laser treatments. Up to 48% of patients taking Iopidine for over 3 weeks develop follicular conjunctivitis.<sup>1,2</sup> Periorcular contact dermatitis was also associated with Iopidine allergy in 62% of the cases.<sup>2</sup> We report a case of an Iopidine allergic reaction



Figure 1 Initial patient presentation demonstrating left upper eyelid ptosis, left lower eyelid ectropion, and diffuse conjunctivitis.

presenting with eyelid ectropion which further progressed to cicatricial entropion.

#### CASE REPORT

A 64 year old man was referred with a 6-8 month history of non-resolving conjunctivitis, epiphora, and resultant left lower eyelid ectropion. The conjunctivitis was resistant to treatment with Ocuflor OS four times daily. As a result, the referring provider added Tobradex (tobramycin) and Naphcon A (naphazoline), and referred him for evaluation. His ocular history was notable for bilateral pterygium excision 2 years earlier and open angle glaucoma. The patient's current ocular medications included Timoptic 0.5% in both eyes twice daily, Iopidine left eye twice daily, and Tobradex in left eye three times daily. Of historical note, the patient began the Iopidine approximately 2 months before developing these symptoms in the left eye. The patient had no known drug allergies. Corrected visual acuities were 20/20 right eye and 20/100 left eye. External examination revealed left upper eyelid ptosis, left lower punctal and eyelid ectropion, and diffuse left eye papillary conjunctivitis (Fig 1).

The Iopidine and the Tobradex were discontinued. The patient began prednisolone (Pred-Forte 1%) left eye every 2 hours in addition to his current regimen of Timoptic and Ocuflor. Within 3 weeks, his left eye improved dramatically. However, he developed a cicatricial entropion with symblepharon, keratinised lower eyelid margin, and persistent left upper eyelid ptosis requiring surgical correction (Fig 2). Tissue samples submitted for histological examination revealed lymphocytic infiltration, admixed with plasma cells, and foci of a haemorrhage within the conjunctiva and subepithelial stroma. Immunohistochemical preparations revealed 50% B cells and 50% T cells, leading to the diagnosis of reactive lymphoid infiltrate.



Figure 2 Left lower eyelid symblepharon which caused entropion 3 weeks after discontinuation of Iopidine and topical steroid treatment.

## COMMENT

Our finding of reactive lymphocytic infiltrates in the conjunctival specimen is consistent with a type IV hypersensitivity reaction and the diagnosis of Iopidine allergy. To our knowledge, this is the first report of an ectropion progressing to a cicatricial entropion resulting from an Iopidine allergy response. Iopidine has been reported to cause upper eyelid retraction and entropion.<sup>3</sup> Similarly, dipivefrin, another adrenergic agent and a topical antiglaucoma medication, has been reported to cause lower eyelid ectropion<sup>4</sup>; however, this ectropion resolved 3 weeks after

drug discontinuation. In our case, the inflammation induced by the topical medication caused the initial ectropion which progressed upon resolution and scar formation to cicatricial entropion. Iopidine induced conjunctivitis can produce both ectropion and entropion.

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Accepted for publication 16 March 1999

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## Various phenotypic expressions of familial aniridia with a *PAX6* mutation

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*Br J Ophthalmol* 1999 83: 987  
doi: 10.1136/bjo.83.8.e987

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