# Surgically induced necrotising sclerokeratitis (SINS) – precipitating factors and response to treatment

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**Abstract**

**The clinical features, treatment, and visual outcome of 52 eyes from 43 patients who developed scleritis following surgery were reviewed. In all patients the scleral inflammation developed adjacent to a surgical wound. Ninety six per cent had necrotising disease and 23% also had evidence of secondary posterior scleritis. Many different types of ocular surgery were implicated and the majority (75%) of the patients had two or more surgical procedures before the onset of the scleritis. Although cataract extraction through a limbal incision resulted in the largest subgroup, scleritis also followed glaucoma, strabismus, and retinal detachment surgery. The latent period between surgery and the appearance of inflammation was short (mean 9 months) except for a small group in whom scleritis occurred many years after squint surgery. Sixty three per cent of patients had evidence of a systemic disease. Early diagnosis and aggressive medical treatment significantly improved the visual outcome. The precipitating factors, pathogenesis, and course of this condition are discussed.**

Scleral inflammation and necrosis are recognised as rare sequelae to ocular surgery with potentially devastating consequences to the eye.[1-5] Arentsen *et al*[1] described four patients who developed marginal corneal ulceration after cataract extraction, and they distinguished the disease from Mooren's ulcer. Lyne and Lloyd Jones[3] described six patients without a previous history of scleral inflammation who developed scleral necrosis at a surgical wound. They observed that necrosis could develop many months after surgery and could progress to involve the whole of the anterior segment. Salamon and co-authors[4] reported four further cases that developed scleritis, peripheral corneal ulceration and sterile infiltrations around Polyglactin sutures following cataract extraction, whose inflammation settled with intensive topical steroids.

The aetiology of postsurgical scleritis is uncertain.[1 2 6-10] However, it has been noted that scleritis develops more frequently following multiple surgical events than after a single operation.[3] This suggests that the condition may be the result of a hypersensitivity reaction directed against an antigen revealed or altered by tissue injury.

The medical records of all patients from a single clinic population who were documented to have developed postsurgical scleritis or sclerokeratitis were reviewed in order to gain a better understanding of the predisposing factors, both local and systemic, and to examine the outcome of the various treatment regimens that were used.

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## Materials and methods

The clinical records were reviewed from a total of 43 patients who had been referred to the scleritis clinic at Moorfields Eye Hospital between 1975 and 1988 and had developed scleritis following ocular surgery. Data were extracted with particular reference to the details of previous surgery, the presence of potential risk factors in the previous medical history, the features of the scleritis, and the treatment required to control the disease. All patients underwent detailed ocular examination using the slit-lamp and indirect ophthalmoscopy. Medical assessment was aimed at the detection of a predisposing disease. Routine investigations included haematology and immunology profiles, serology (VDRL and TPHA), serum uric acid estimation, chest *x*-ray and, in most cases, ultrasonic examination of posterior coats of the eye. Clinical photographs and anterior segment fluorescein angiograms were also reviewed, where available.

Throughout this period the diagnostic classification of scleritis used was that recommended by Watson and Hayreh.[11]

## Results

The series consisted of 52 eyes of 43 patients, none of whom had a history of scleritis prior to surgery; 13 were male (mean age at presentation 52·3 years, range 26 to 75 years) and 30 were female (mean age 68·2 years, range 32 to 87 years). Scleritis developed after one operation in 11 patients (25·6%) while the remaining 32 subjects (74·4%) had undergone two or more surgical procedures before the onset of the disease. The nine patients who developed bilateral scleritis had all undergone bilateral ocular surgery. The wound site was intimately related to the site of the subsequent disease process in all the eyes.

The duration of the latent period between surgery and the onset of scleral inflammation varied from 40 years to the first postoperative day (mean duration 39·6 months). However these are weighted by the five cases in whom squint surgery was the only procedure (mean 21·7 years; range 6·5 to 40 years) compared with the remaining 38 cases (mean latency: 5·7 months; range 1 day to 3·5 years).

Necrotising anterior scleritis or sclerokeratitis was identified in 49 eyes (94·2%) (see Figs 1 to 6); the remaining three eyes having nodular scleritis. This is significantly higher than the incidence of necrotising disease in the overall

*Table 1 Comparison of scleritis type between 290 consecutive scleritis clinic patients 1986–88 and all whose scleritis followed ocular surgery 1975–88*

| | Scleritis clinic | Post surgery |
|---|---|---|
| Diffuse | 105 (36%) | 0 |
| Nodular | 98 (34%) | 3 (5·8%) |
| Necrotising | 55 (19%) | 40 (94·2%) |
| Posterior | 32 (11%)* | 12 (23·1%)† |

*Primary disease occurring posterior to equator.
†Secondary involvement of sclera in posterior segment and may be anterior to the equator.

*Table 2 Types of surgery*

*Single procedure (n=11)*
5 single strabismus corrective procedures
5 unilateral cataract extraction
1 scleral trauma

*Multiple procedures (n=32)*
7 bilateral cataract extraction
8 cataract extraction and secondary ocular surgery (strabismus correction, YAG capsulotomy, ruptured section repair, aphakic retinal detachment repair
5 multiple retinal detachment surgery
3 bilateral trabeculectomy
2 multiple squint surgery
2 anterior segment trauma
1 cataract extraction following herpes zoster ophthalmicus
1 squint preceded by orbital decompression
1 laser trabeculoplasty, trabeculectomy
1 bilateral PI, anterior chamber tap
1 goniotomy, squint, keratoplasty, retinal detachment repair

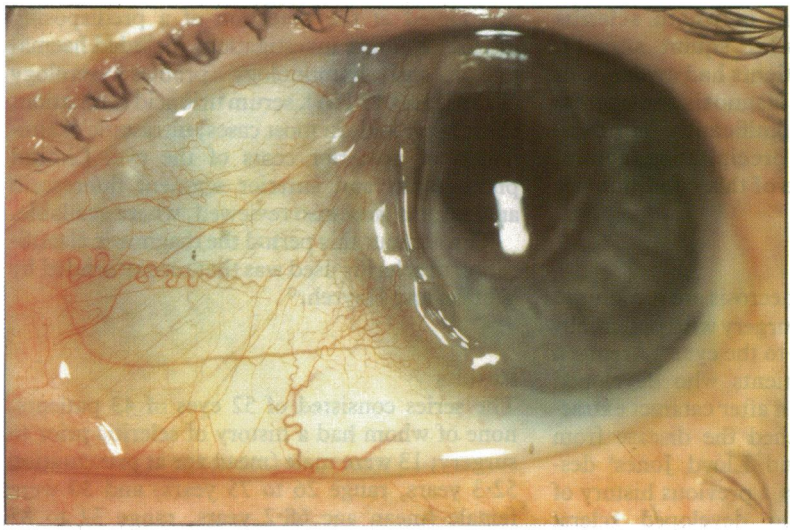

*Figure 1 Inactive gutter following control of a sclerokeratitis episode with onset after cataract surgery.*

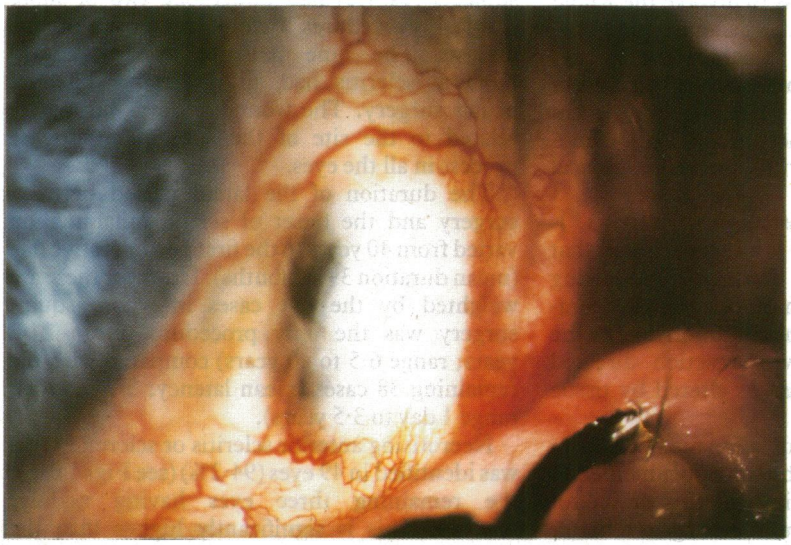

*Figure 2 Localised area of necrotising scleritis following squint surgery.*

scleritis clinic population[12] (see Table 1) and has major therapeutic implications. However, at initial clinical evaluation less than 60% could be definitely identified as having necrotising scleritis, with the remainder being recognised either by further examination over the following weeks or, in some equivocal cases, the diagnosis was made following anterior segment fluorescein angiography.

The incidence of posterior scleritis was also higher than any previously reported series[13 14] with 12 eyes (23·1%) developing posterior extension of the inflammatory process. Posterior inflammation tended to be localised to the periphery and involved the posterior pole in only two eyes. These findings were confirmed by ultrasonography. All responded to treatment with systemic steroids and posterior scleral inflammation was not a significant contributory factor to visual loss in any of these patients.

A wide variety of surgical procedures preceded the onset of scleritis (see Table 2) which most commonly occurred at the site of incision for cataract extraction (25 eyes, 48%). Of these, 20 (80%) followed limbal incision in which the posterior lip was the main area of involvement, unlike the series of Arentsen *et al*[1] where the anterior lip was mainly affected in all four cases. In these 20 cases the inflammatory process remained confined to the superonasal quadrant in 65%. Five other patients had corneal sections. In two of these, who had necrotising scleritis with minimal corneal involvement, the corneal sutures were found to have entered the sclera. The three remaining patients had predominantly corneal guttering extending from a corneal section with secondary scleral involvement; one patient had serial fluorescein angiographic evidence of gross limbal and scleral ischaemia moving ahead of an advancing corneal gutter (Fig 1). Although the cataract incision was central to the inflammatory process in all 25 cases it is clear that minor subsequent surgical procedures (suture removal, YAG capsulotomy and repair of wound leak) were the provocative insult in six of these.

Nine patients (12 eyes) developed scleritis at the site of previous squint surgery. Unlike the patients so far discussed, in whom the onset of scleritis shortly followed the surgical insult, five of these patients had a single strabismus correction procedure in childhood with onset of scleral disease many years later (mean interval 21·7 years) (Fig 2). Of these five patients, four were female and four had previously undiagnosed immune abnormalities. This included two who were found to be rheumatoid factor positive and who later developed rheumatoid arthritis, and two whose scleritis was preceded by seronegative acute polyarthropathy and who were found to have high circulating immune complexes but no further disease manifestations. The four other patients underwent multiple surgery in adulthood with strabismus surgery being the final procedure (that is, for diplopia following cataract extraction) provoking localised scleritis after a much shorter interval (mean 10 weeks). The area surrounding lateral rectus insertion was selectively involved in nine of 12 eyes (75%) despite seven having had concurrent surgery to ipsila-

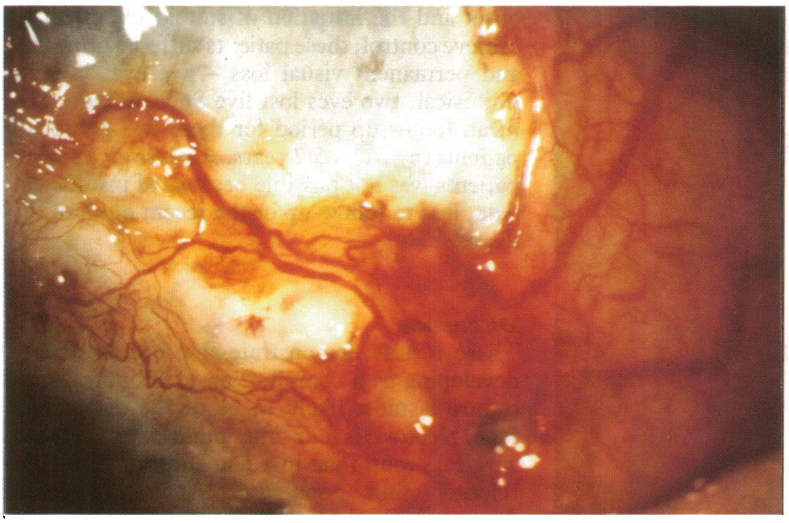

*Figure 3 Scleritis following trabeculectomy showing both early and advanced areas of necrosis. A provisional diagnosis of Wegener's granulomatosis was subsequently confirmed.*

teral medial rectus suggesting increased vulnerability of the vascular bed in this region.

Seven cases of necrotising inflammation followed retinal detachment surgery. In four of these scleritis occurred at the explant site and the subsequent management included removal of explant in three cases with rapid resolution of the scleritis. Two further cases occurred at vitrectomy entry sites and another patient developed scleritis at the site of previous cataract surgery within weeks of an uncomplicated repair of an aphakic retinal detachment.

Four patients with glaucoma presented at a mean interval of 12 months following trabeculectomy with an inflamed non-filtering bleb and rapid progression of localised necrotising scleral disease (Fig 3). Scleritis was also seen in one case after surgical iridectomy.

Adequate documentation of associated systemic disease was available for 36 patients (Table 3). In 11 of these 36 patients no associated disease had been noted prior to the onset of scleritis but was revealed by subsequent investigation. Fourteen patients had serological and/or clinical evidence of a systemic collagen disease, five had a thyroid disorder (two in association with collagen disease), four were diabetic and one patient was hyperuricaemic. No evidence of any systemic disorder was found in 13 other patients and in the remaining seven cases insufficient data precludes comment.

*Table 3 Associated disease*

| | | | |
|---|---|---|---|
| 4 | diabetes mellitus | | |
| 5 | thyroid disease | 4 | hyperthyroid (2 also with collagen disease) |
| | | 1 | hypothyroid |
| 14 | collagen disease | 7 | rheumatoid arthritis |
| | | 3 | Wegener's granulomatosis |
| | | 1 | polyarteritis nodosa |
| | | 2 | seronegative polyarthropathy |
| | | 1 | polymyalgia rheumatica |
| 1 | hyperuricaemia | | |
| 1 | herpes zoster ophthalmicus | | |
| 13 | no known associated disease | | |

Postoperative infection and herpes zoster ophthalmicus were implicated in one case each. As found in earlier studies[1 3 9] the use of a specific suture material could not be related to the development of the disease.

The scleritis was controlled in all patients and no eyes were excised. Non-steroidal anti-inflammatory agents were sufficient to control the disease in only three patients despite their use as the initial treatment regimen in half of the group. For 40 patients high dose systemic steroid therapy (60 to 80 mg daily) was an essential part of their management and was usually followed by rapid resolution and healing (Fig 4); all needed low dose maintenance therapy for periods ranging from 2 months to 6 years. In addition to oral prednisolone, 11 patients were given at least one pulse of intravenous methylprednisolone (500 mg) and 15 patients needed adjunctive therapy with immunosuppressive agents – oral or intravenous cyclophosphamide or oral azathioprine (Table 4). For three of the four patients with retinal detachment with necrosis at the explant site control was only achieved following high dose systemic steroid treatment *and* the removal of the explant. Perforation through necrotic sclera or cornea occurred in eight (Fig 5) patients necessitating surgical excision of necrotic tissue and tectonic reconstruction (six corneoscleral grafts, one scleral graft, one corneal patch graft).

Reactivation of the disease requiring re-treatment was seen in 16 patients either on reduction of steroid dosage shortly after the acute stage or, in some patients, after a long remission off all treatment. Those patients who had recovered from SINS and required further ocular surgical procedure were given perioperative pulsed methylprednisolone to protect against recurrence of necrotising disease.

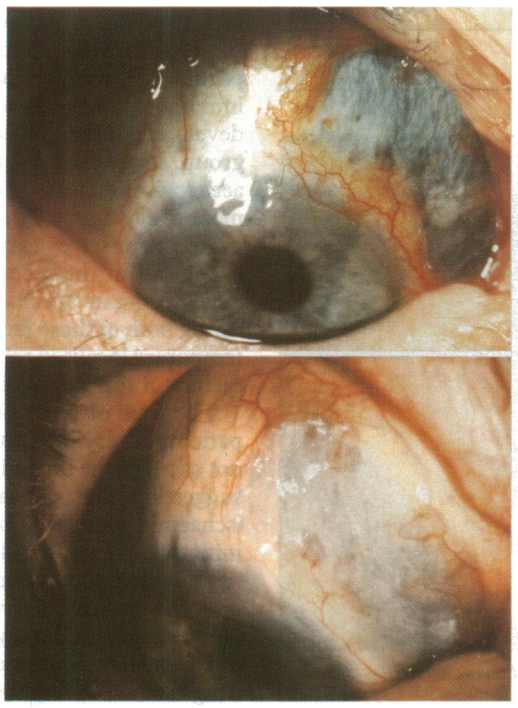

*Figure 4 Upper figure illustrates necrosis with onset 4 weeks after removal of a subconjunctival nylon suture (cataract extraction was performed 5 months previously). Lower figure shows early resolution 9 days later on high dose systemic steroids.*

*Table 4 Treatment required to control disease*

| | |
|---|---|
| Non-steroidal anti-inflammatory agents | 3 |
| High dose systemic steroids | 40 |
| Pulsed intravenous steroids | 11 |
| Oral cytotoxic agents | 15 |
| Surgical reconstruction | 8 |
| Removal of surgical explant (retinal detachment) | 3 |

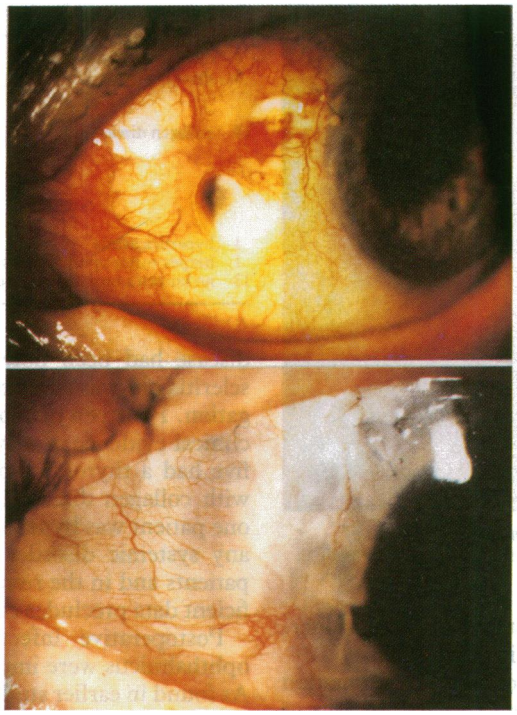

*Figure 5 Upper figure: scleritis close to limbal section. Resolution with a short course of high dose systemic steroids was sustained for 1 year when recurrence led to perforation requiring scleral patch graft and treatment with cyclophosphamide and pulsed methylprednisolone (lower figure).*

There was a clear-cut relationship between aggressive early medical treatment and successful visual outcome (see Table 5). Of the 24 patients who had high dose systemic steroid treatment within 1 month of the appearance of symptoms the mean visual loss was Snellen equivalent 0·5 lines (range 0 to 3 lines lost). In seven other patients with necrotising disease there was an interval of at least 3 months between onset and the initiation of steroid treatment to achieve control; these patients suffered profound and permanent visual loss – five eyes became phthisical, two eyes lost five Snellen lines. The mean follow-up period for these two groups of patients ($n=31$) is 5·2 years. Analysis of 12 other patients was not possible because of insufficient data, loss to follow-up or the recent onset of the disease.

*Table 5 Long term visual outcome related to the interval between onset of scleritis and initiation of high dose steroids*

| *Interval* | *Number of patients* | *Mean Snellen loss (>5 year follow-up)* |
|---|---|---|
| <1 month | 24 | 0·5 lines (range 0–3) |
| >3 months | 7 | 7·0 lines (range 5–9) |

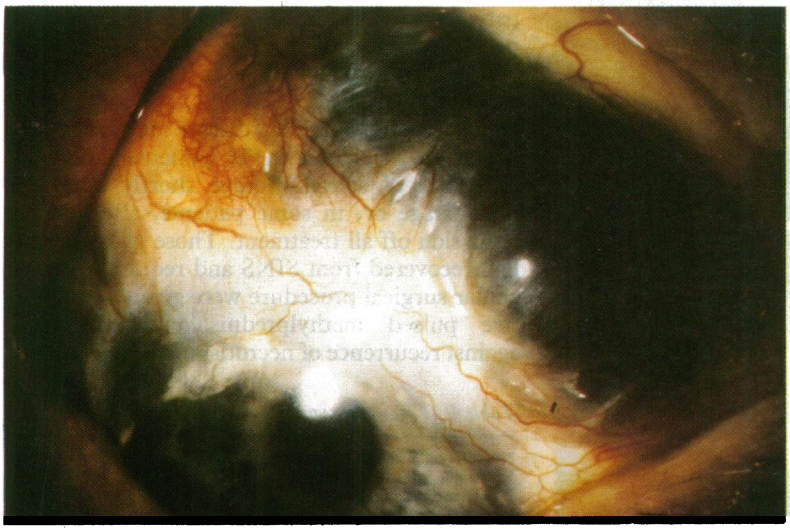

*Figure 6 Extreme scleral thinning with staphyloma formation following necrotising scleritis related to second cataract surgery.*

## Discussion

These results demonstrate that scleral disease developing as a complication of a surgical procedure is most likely to be of the necrotising type. Necrosis is four times more common in the surgical group than in a non-surgically induced scleritis clinic population. Anterior segment fluorescein angiography demonstrates that the vascular closure is limited to the immediate vicinity of the wound in most cases. Seventy five per cent of patients developed disease after multiple ocular surgical procedures, some of them minor, with a mean interval of 9 months and a 40% association with a predisposing medical disorder. The remaining population developed disease after a single surgical episode with a mean interval of 9·5 years and a 90% association with a predisposing medical disorder. This group further differed from the multiple surgery group in having a fivefold greater incidence of background collagen disorder where scleritis tended to be but one of a number of the acute manifestations of underlying systemic disease.

Overall, 63% had an underlying medical disorder of which the commonest group was connective tissue disease. Eight patients had evidence of organ-specific autoimmune diseases such as thyroid disorder or diabetes; 70% of patients were female which is in keeping with the increased incidence of autoimmune diseases in females. The exact relationship of the medical disorder to the development of postoperative scleritis is unknown but systemic vasculitis is a feature of the collagenoses and this can occur in the blood vessels of the deep episcleral venous plexus. Moreover, patients with one autoimmune disease have an increased risk of developing other diseases of the autoimmune group, suggesting that there may be two separate aetiological factors predisposing to the development of the disease. In the first group, the blood vessels themselves may be affected as a primary event and in the second there is a tendency to develop organ specific autoreactivity. Complicating both of these factors is the effect of at least temporary localised relative ischaemia as a consequence of the surgical incision.

The time of onset of scleral necrosis in these patients is very interesting. In most cases it does not occur in the immediate postoperative period, suggesting that primary vascular closure and ischaemia alone are unlikely to be important initiating events. In addition the rapid response to immunosuppressive drugs implies that the immune system is actively involved at least in the perpetuation and maybe the initiation of the inflammatory response. Neither corticosteroid drugs nor cyclophosphamide are selective

immunosuppressants and therefore do not give any clues as to the involved arm of the immune system, with both T cells and B cells being affected by these drugs.

The histological appearance at the edge of a lesion of necrotising scleritis is said to be of a delayed type of hypersensitivity response,[7] which is known to require the presence of sensitised CD4+ T cells. The antigen in the vicinity of the sclera to which these T cells become sensitised has not been identified, but it is possible that either the surgical trauma or the temporary ischaemia alters or exposes tissue antigens to which the immune system is not normally exposed and which are therefore recognised as foreign. Circulating antibodies to scleral collagen are rarely detected in these patients, but circulating immune complexes have been noted in some. The relevance of this is unknown but may contribute to the vasculitis after its initiation. Since the pathological process is usually that of a necrotising inflammation, its pathogenesis may be different from the more usual types of scleritis and subclinical ischaemia may be a pivotal factor. It is likely that ischaemia plays an important role in the scleritis that follows encirclement for retinal detachment since removal of the buckle usually results in reduction in and healing of the scleral disease. Likewise significant local ischaemia is a known complication of squint surgery, and in our patients developing scleritis following cataract surgery it is much more frequently associated with limbal approach than following corneal section – perhaps reflecting the greater relative vascular disruption.

It is also possible that the immune response is triggered elsewhere and becomes manifest in the eye for other reasons. (This would seem to be the case in those patients who had an interval of many years between surgery – usually a single uncomplicated procedure – and onset of scleritis, in most of whom the ocular inflammatory episode was almost concurrent with other early systemic manifestations of immune disorders such as rheumatoid arthritis, Wegener's granulomatosis, or polyarteritis.)

First, immune complexes which are formed as a consequence of a problem elsewhere in the body could be deposited in the deep episcleral blood vessels which are affected by the surgical procedure. This could subsequently initiate the inflammatory response in the eye over a period which would appear unrelated in time and place to the initial stimulus. Alternatively, there could be molecular mimicry/cross-reactivity between an ocular antigen and either a tissue antigen elsewhere in the body or a microbial antigen (that is, ankylosing spondylitis and *Klebsiella*; experimental allergic uveitis (EAU) and fungus).[15 16]

Whatever the aetiology of this devastating scleral inflammation, the paramount message from the results presented here is that appropriate treatment must be started as early as possible. Non-steroidal anti-inflammatory agents are not usually effective in the face of this disease so that immunosuppressive treatment with high dose corticosteroids and cytotoxic drugs as necessary should be used at presentation and their instigation should not be delayed. Should the disease progress in spite of adequate immunosuppression surgical replacement of damaged tissue must be considered. With a greater understanding of the immune mechanisms involved, it may be possible to use more selective immunosuppressive agents in the future and spare these patients some of the side effects of this necessary treatment.


1 Arentsen JJ, Christiansen JM, Maumenee AE. Marginal ulceration after intracapsular cataract extraction. *Am J Ophthalmol* 1976; **81**: 194–7.
2 Bloomfield SE, Becker CG, Christian CL, Nauheim JS. Bilateral necrotising scleritis with marginal corneal ulceration after cataract surgery in a patient with vasculitis. *Br J Ophthalmol* 1980; **64**: 170–4.
3 Lyne AJ, Lloyd-Jones D. Necrotising scleritis after ocular surgery. *Trans Ophthalmol Soc UK* 1979; **99**: 146–9.
4 Salamon SM, Mondino BJ, Zaidman GW. Peripheral corneal ulcers, conjunctival ulcers, and scleritis after cataract surgery. *Am J Ophthalmol* 1982; **93**: 334–7.
5 Grindle CF, Marshall J, McLeod D, Clarke E, Fison LG. Complications of explants used in retinal detachment surgery. *Mod Probl Ophthalmol* 1979; **20**: 219–20.
6 Watson PG. Doyne Memorial Lecture, 1982. The nature and treatment of scleral inflammation. *Trans Ophthalmol Soc UK* 1982; **102**: 257–81.
7 Sevel D. Necrogranulomatous scleritis, a clinical, pathological, and experimental study. MD Thesis, University of London. 1966.
8 Watson PG, Hazleman BL. *The sclera and systemic disorders.* London: Saunders, 1976, Chapter 6: 171–205.
9 Apt L, Costenbader FD, Parks MM, Albert DG. Catgut allergy in eye muscle surgery. *Arch Ophthalmol* 1961; **65**: 474–80.
10 Hembry RM, Playfair J, Watson PG, Dingle JT. Experimental model for scleritis. *Arch Ophthalmol* 1979; **97**: 1337–40.
11 Watson PG, Hayreh SS. Scleritis and episcleritis. *Br J Ophthalmol* 1976; **60**: 163–91.
12 Tuft S. Scleritis. (In press).
13 Calthorpe CM, Watson PG, McCartney ACE. Posterior scleritis: a clinical and histological survey. *Eye* 1988; **2**: 267–77.
14 Benson WE. Posterior scleritis. *Surv Ophthalmol* 1988; **32**: 297–77.
15 Ebringer R, Cawdell D, Ebringer A. *Klebsiella* pneumonia and acute anterior uveitis in ankylosing spondylitis. *BMJ* 1979; **1**: 383.
16 Singh VK, Yamaki K, Danoso L, Shinohara T. Sequence handling between yeast histone H3 and the uveopathogenic site of S-antigen. *Cell Immunol* 1989; **119**: 211–21.