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REVIEW

The impact of new methods of investigation and treatment on the understanding of the pathology of scleral inflammation

P Watson[1,2,3,6] and A Romano[4,5,6]

Abstract

Recent advances in the understanding of the initiation and perpetuation of the immune response strongly suggest that all forms of noninfective immunologically induced scleral inflammation have a common origin. Analysis of the progress of patients with scleritis corroborates the current clinical classification that, together with studies of the immunohistology fluoresceine/ICG angiography, 3D proteoglycan, and keratan sulphate electron microscopy of scleritis, strongly suggests that from the initiation of the inflammatory process, necrotizing scleritis and diffuse and nodular scleritis not only pursue a different course but also have a different pathogenesis; nonnecrotizing scleritis being the consequence of an auto immune response, whereas necrotizing scleritis being the complication of an already present (if not always manifest), systemic immune-mediated systemic disease and its associated vasculitis. The increasing imaging capacity of anterior segment ocular coherence tomography (OCT) and *en face* OCT enables the changes occurring in the sclera during the course of the disease to be observed for the first time. These observations suggest that the inflammatory changes involve the potential suprachoroidal space between choroid and sclera, an observation supported by the presence of subscleral granulomas on histopathology. New imaging techniques have also been able to explain the changes seen in the cornea as a complication of scleritis. These findings have implications for investigation and the treatment of these conditions.
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Introduction

Although scleral inflammation is uncommon, accounting for only one new patient in every thousand seen in the general hospital or clinical practice,[1] it needs to be accurately diagnosed to ensure that those who have potentially life-threatening disease are treated urgently and effectively and the others are not given potentially dangerous or inappropriate medication.

The presentation, investigation, and treatment of most severe forms of scleral inflammation have been extremely well covered in recently revised texts by Watson *et al*,[2] Sainz de la Maza *et al*,[3] the recent review articles by Wieringa *et al*,[4] by Watson and Young,[5] and the very extensive and thorough review of Wakefield *et al*,[6] and hence this information will not be reiterated here.

The classification of the clinical manifestations of scleral inflammation that was proposed in 1968 (see Watson *et al*[7]) (Figure 1) has been used since then to differentiate between the various forms of presentations of inflammation of the sclera and thus act as a guide to the appropriate treatment. However, there are several questions that still need to be answered.

The general questions are:

- Have the newer methods of investigation and potential treatments available for the management of scleritis altered the original classification in any way?
- Are necrotizing scleritis and nonnecrotizing diffuse and nodular scleritis manifestations of the same pathological process or different conditions?

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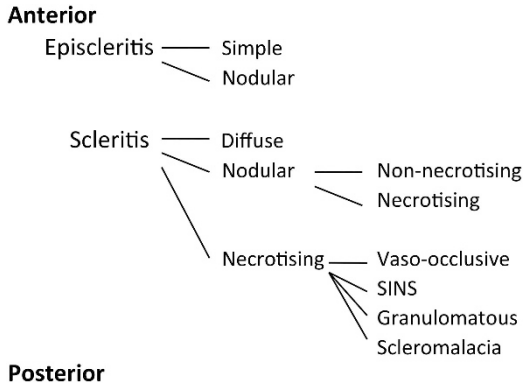

Figure 1 The current classification of noninfective scleral inflammation modified from that proposed in 1968 (see ref. 2 pp 154–160). Apart from the additional differentiation between the nonnecrotizing and the necrotizing form of nodular scleritis, this classification remains correct. Posterior scleritis is non-necrotizing even when the choroid is also affected. SINS is scleritis following trauma often surgically induced.

More specifically:

- Why does the inflammation occur in sclera, a tissue that is structural in nature and has no direct blood supply?
- What is it that initiates the immune response that leads to scleral inflammation?

With regard to the corneal complications:

- How is it that the cornea becomes involved in scleral disease when the structure and cellular constitution are so different?
- Why should the cornea react in different ways in patients with apparently similar scleral disease?

All of these questions can now be answered thanks to new methods of imaging of the scleral and cornea *in vivo* and revelations from researches in other immunologically induced conditions.

Are necrotizing scleritis and nonnecrotizing diffuse and nodular scleritis manifestations of the same pathological process or different conditions?

Although there are different clinical presentations and different types of vascular involvement in necrotizing disease, such as the differences found in the systemic vasculitides and those seen in rheumatoid arthritis, it could well be that diffuse and nodular disease and necrotizing disease have a similar underlying pathology. However, observations of the clinical course of the inflammatory process and the histological investigations of Riono *et al*[8] (confirmed by the examination of the pathological specimens in the Wilmer Institute Baltimore) (see ref. 2 pp 154–160) indicate that there are differences at every stage in the progress of the disorders up to the final stages of the disease between those who present with nonnecrotizing scleritis and those who develop necrotizing disease. The new imaging methods of a speckle noise reduction algorithm and increased scan length modified RTVue anterior segment ocular coherence tomography (OCT; Optovue, Fremont, CA, USA) and *en face* OCT together with anterior segment fluorescein and indocyanin green (ICG) angiography and the results of the recent methods of treatment pose a hypothesis that necrotizing and nonnecrotizing scleritis have different aetiologies with differing courses and prognosis; something that considerably influences not only our understanding of the underlying mechanisms but also the management of the various manifestations of scleral inflammation.

Clinical differences

Although there are bound to be overlaps and misdiagnoses in the assessment of all the varieties of scleritis particularly at the first presentation, it is almost always possible to distinguish between infective scleritis, noninfective necrotizing scleritis, and the less severe diffuse and nodular anterior sclerits of immune-mediated origin when the patient is first seen. Posterior scleritis is invariably nonnecrotizing unless the destructive process has extended from the anterior segment. Acute scleral inflammation in the posterior segment induces an exudative retinal detachment but no necrosis of the sclera. Structural changes can occur that are not due to inflammation as with the severe scleral thinning encountered during surgery for retinal detachment because of myopic or post-wound healing changes in the sclera. In the vaso-occlusive form of necrotizing scleritis, there is often a progressive obliteration of the vascular networks leading to gradual removal of scleral tissue without intense inflammation. Anterior and posterior uveitis is not an accompaniment of scleral disease except in its very severest form.

Presentation

Severe pain that wakes the patient at night, radiating to the face and jaw and gradually improving during the day, is the hallmark of all forms of scleritis except scleromalacia perforans (scleromalacia perforans is now a very rare condition seen in the late vasculsitic stages of rheumatoid arthritis in which the sclera disintegrates leaving bare choroid exposed). Although the onset of necrotizing scleritis is acute, the pain severe and accompanied by the rapid onset of severe inflammation,

obviously demanding immediate care and attention, the presentation of noninfective diffuse and nodular scleritis may take days to develop with increasingly severe or intermittent pain such that referral is often delayed for a considerable period.

Demographics are of little help in distinguishing one group from another at the onset of the disease except that necrotizing scleritis is much more often bilateral than non necrotizing disease. Overall, scleritis affects all races and creeds equally with a female predominance and can occur in anyone from 9 to 96 years of age. There is no genetic association or HLA association peculiar to any form of scleritis that does not accompany another systemic disease.

Course

Left untreated, the course of necrotizing scleritis is rapid, inexorable, and destructive, whereas nonnecrotizing disease is slowly progressive and even self-limiting, only in the rare cases leaving visible changes in the affected sclera.

If the scleritis recurs, the type of scleritis that has been diagnosed at its onset remains the same even if it recurs at the initial site of the disease or elsewhere (Table 1). A change from nonnecrotizing scleritis to necrotizing scleritis was seen in only 13 of the 104 patients. Of the 10 patients who changed from nodular to necrotizing scleritis, 9 were later found to have an overt underlying systemic disease.

Associated disease

A cause or underlying disease is rarely found in those who have nonnecrotizing noninfectious scleritis. When found, it is usually associated with a sero-negative condition such as Reiter's or Behcet's disease.

In contrast, necrotizing scleritis is associated with systemic diseases, in particular the vasculitides or autoimmune conditions associated with vasculitis. Scleritis is most commonly seen in rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's granulomatosis), polyarteritis nodosa, and relapsing polychondritis. Occasionally, it is the direct result of viral, parasitic, or bacterial infection, particularly leprosy in regions where this disease is endemic. Surgically induced necrotizing scleritis (SINS) can occur after any form of trauma. Where it follows surgery, it is noticed that the post-operative inflammation is slow to settle or even gets more intense. In SINS the scleral inflammatory response is almost always necrotizing, severe, and very resistant to treatment. Sometimes the scleritis occurs, not at the site of the recent procedure, but at the place of previous trauma such as a childhood strabismus operation.

Table 1 Number of patients changing clinical groups during recurrence of scleritis

	(104 Patients)
No change	66
Diffuse to nodular	12
Nodular to necrotizing	10
Posterior to nodular	4
Posterior to diffuse	3
Diffuse to necrotizing	3
Nodular to diffuse	2
Necrotizing to nodular	2
Nodular to pseudotumour	2

Investigations

The different types of nodular scleritis have, until now, been difficult to diagnose because some are due to a localized but intense form of benign scleral inflammation, some present as an early manifestation of necrotizing scleritis, and others are infective. The advent of speckle noise reduction algorithm and increased scan length Fourier domain anterior segment OCT and *en face* anterior segment OCT developed by one of us (André Romano) together with anterior segment ICG angiography has led to a step change in diagnosis. Given the right tools the diagnosis can be made as soon as the patient presents.

Anterior segment OCT

An adjusted algorithm for anterior segment OCT imaging is a major advance in the ability to confirm the clinical diagnosis of all the major forms of scleritis. The high -resolution images expose the sclera posteriorly to the rectus muscle insertion and hence can show the full extent of the inflammatory process (Figure 2).

In diffuse anterior scleritis there is a localized area of inflammatory cells usually adjacent to dilated vessels. The oedema extends throughout the inflamed area up to the limbus including the episclera and about half the thickness of the sclera. The collagen fibres are separated but otherwise undamaged (Figure 3).

Scleral nodules can be shown to be 'necrotizing' or nonnecrotizing or the result of infection. In the less severe presentations, the scleral fibres are simply separated (Figure 4), even though the inflammation may be the full thickness of the sclera (Figure 5). In the more severe forms (often associated with systemic disease), the centre becomes liquefied. This confirms to what has been noticed many times in the past when on attempted biopsy on incision the liquid content of the nodule escapes leaving only bare choroid (see ref. 2 p 336, Figure 12.20). In nodules with a necrotic centre, the collagen fibres within the nodule become aggregated, losing their

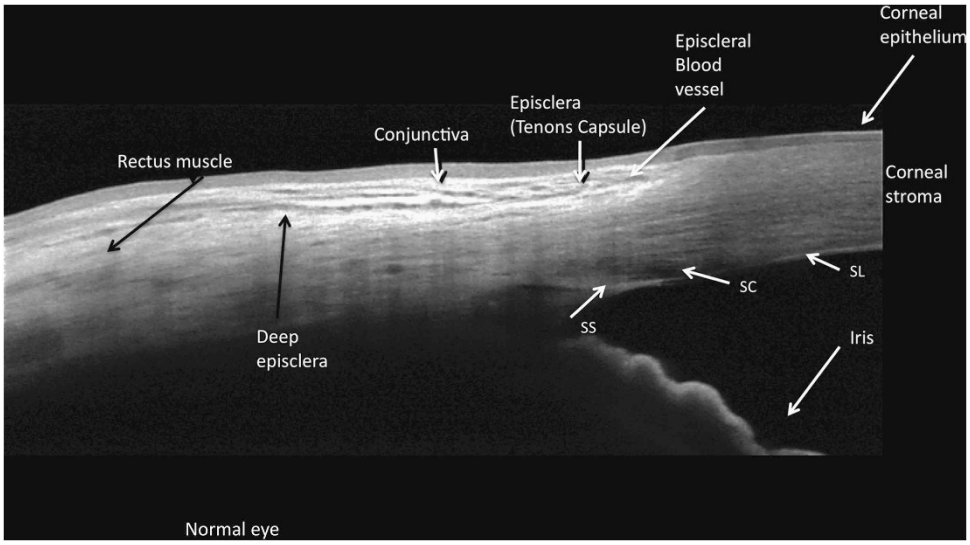

Figure 2 Normal anterior sclera, cornea, and chamber angle as seen with the new algorithm for the anterior segemnt OCT. SS, scleral spur; SC, Schlemm's canal; SL, Schwalbe's line.

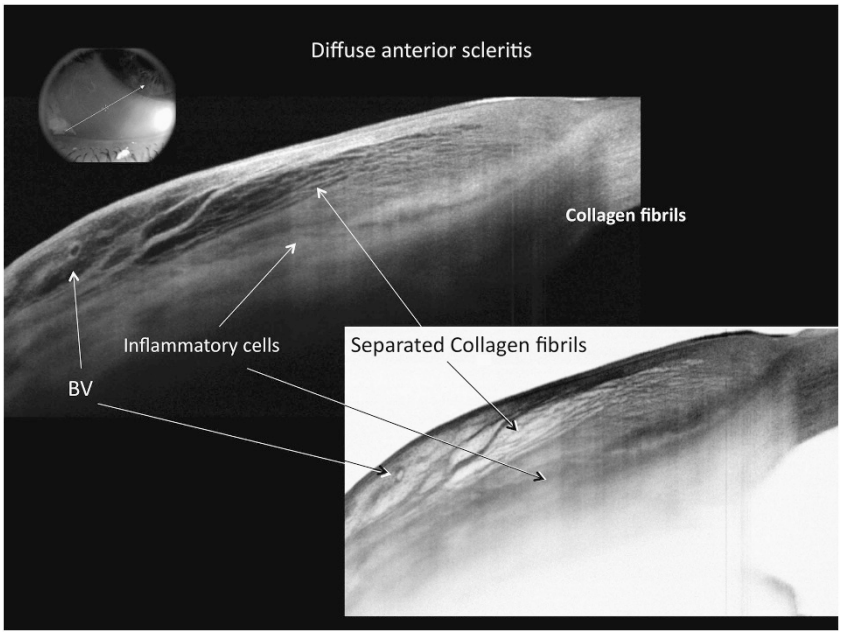

Figure 3 Diffuse anterior scleritis. Anterior segment OCT. There is marked oedmea of the sclera with separation of the collagen fibres and infitration with inflammatory cells in the deeper layers of the sclera. BV, blood vessels.

proteoglycan coat and giving a high reflectance to the image. No individual fibres can be distinguished in the region of the highly reflective image (Figure 6). The high reflectance and loss of fibres becomes even more obvious when destruction of the tissue takes place in necrotizing scleritis. Dr Romano has noticed that the cellular infiltrates develop deep in the sclera (Figure 3) and that in necrotizing scleritis the erosion of the deeper layers of the sclera becomes apparent before anything is visible on the surface of the sclera (Figure 7).

Further development of *en face* OCT has the opportunity to be able to confirm to this observation. The advantage of OCT is the ability to generate depth resolved *en face* images with intensity integrated over a small depth range to visualize scleral structures layer by layer. In Figure 8 the *en face* image of 30 μm thick slab immediately under the conjunctiva depicts the tortuous superficial episcleral vessels. As the scanning slabs move deeper the posterior scleral vessels become more evident as well as a hyporeflective image that indicates

destruction of the posterior surface of the sclera. This suggests that there is an intense inflammatory response involving the sclera and the vessels deep to the sclera at the site of the superficial visible destructive changes.

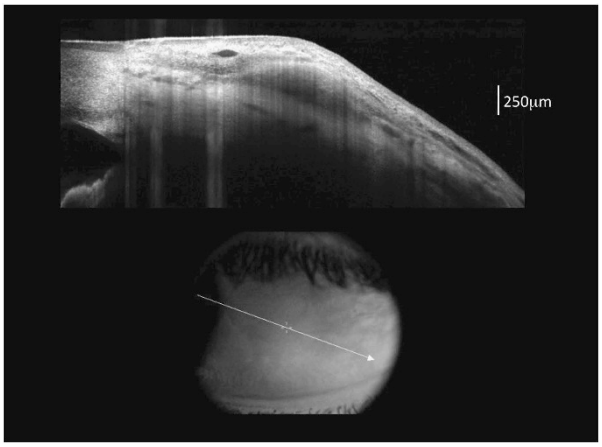

Figure 4 Nonnecrotizing nodular scleritis. Anterior segment OCT. The nodule consists of extracellular fluid. The collagen fibres are separated but remain distinct. There is no necrosis of tissue.

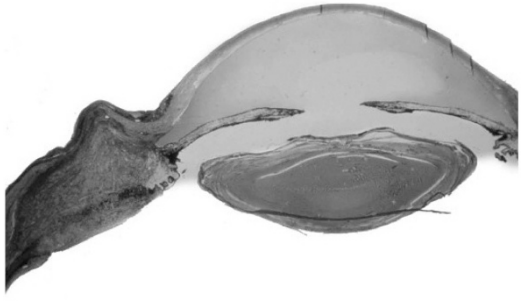

Figure 5 Histology of a nonnecrotizing scleral nodule. The inflammation affects the whole thickness of the sclera.

This is the first time that it has been possible, although imperfectly at present, to observe changes deep to the sclera during the course of the disease. The findings suggest that the changes seen at the surface in scleral inflammation are accompanied by, or even preceded by, similar changes in the potential suprachoroidal space between choroid and sclera (the space accessed in the cyclodialysis operation). This can explain the subscleral granulomas seen universally in the histopathology of eye enucleated from patients with both anterior and posterior scleritis (see ref. 2 p 155, Figures 7.2, 7.3, 7.5).

An extension of this technique using phase variance OCT has the potential to discriminate between different classes and activation of inflammatory cells that carry different charges. This may depend on being able to combine the imaging with tagged markers for each cell subclass as well as utilizing energy sourcing such as the Warburg effect[9] for activation. If this is successful, then specific rather than undirected treatments can be given.

Histology

The sclera is composed largely of type 1 collagen and some elastic tissue. The collagen fibrils are surrounded by proteoglycans that encircle the fibril, run axially along its length, and join one fibril to the next (Figure 9, lower panel). The predominant glycosaminoglycan is chodroitin sulphate/dermatan sulphate. Its structure is maintained by fibrocytes (sclerocytes) that are in contact with each other via cellular processes. The only other resident cell within the sclera is the resident tissue macrophage. There is no direct blood supply to the sclera; the nutrients, which includes the immunoglobulins, arrive by diffusion from the vessels of the choroid, ciliary body and the superficial anterior ciliary arteries (Figure 10).

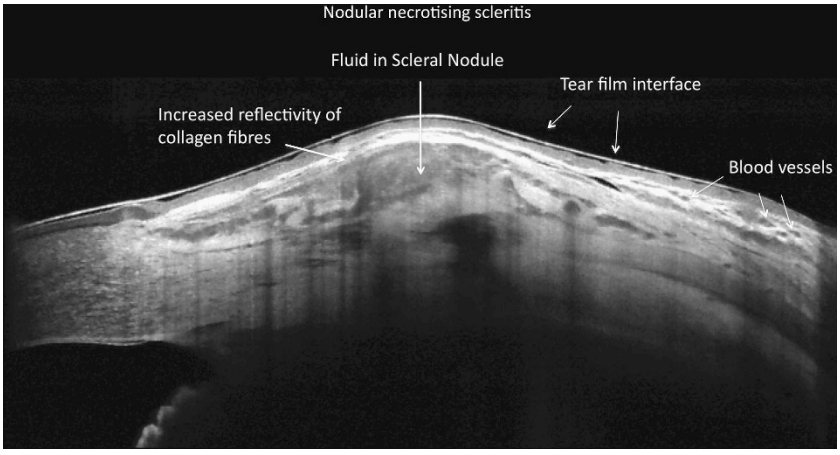

Figure 6 Necrotizing nodular scleritis. Anterior segment OCT. There is hyperreflectivity of the episcleral and deep tissues. The hyporeflectivity of the scleral nodule shows that the deep layers of the nodule are liquefied and interpersed with blood vessels.

Microscopic and electron microscopic studies of biopsy specimens from patients with simple and nodular episcleritis have been totally noncontributory in elucidating the aetiology of these conditions. The inflamed area is packed with lymphocytes and a few other inflammatory cells, but there are no mast cells, plasma cells, or eosinophils.

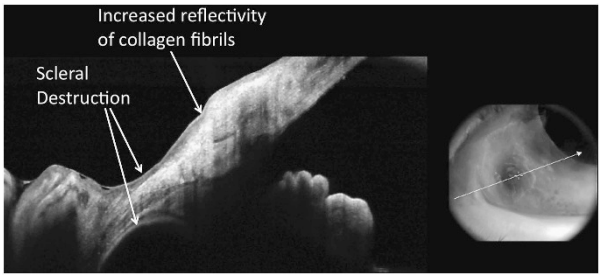

Figure 7 Necrotizing scleritis. Apart from the obvious loss of tissue the collagen fibres are aggregated together, indicating a loss of the proteoglycan coat. There is not only erosion of the superficial tissues but also under surface of the sclera.

Because biopsy of the sclera is undesirable, most of the information regarding the histopathological appearances of scleral disease comes from enucleated specimens of necrotizing scleritis. These confirm that even in the most severe disease the anterior segment is primarily involved and that purely posterior segment disease is very unusual. The findings of Riono *et al*[8] (confirmed by the study of the specimens in the pathology laboratory of the Wilmer Institute in Baltimore) (see ref. 2 pp 155–161) in eyes that were enucleated because of the secondary complications of glaucoma, retinal detachment, choroidal involvement, uveitis, and vascular occlusion had a histological appearance of nonzonal diffuse scleral inflammation and had no association with systemic disease. However, those with zonal necrotizing granulomatous scleral inflammation, with the histopathological characteristics of 'fibrinoid necrosis'

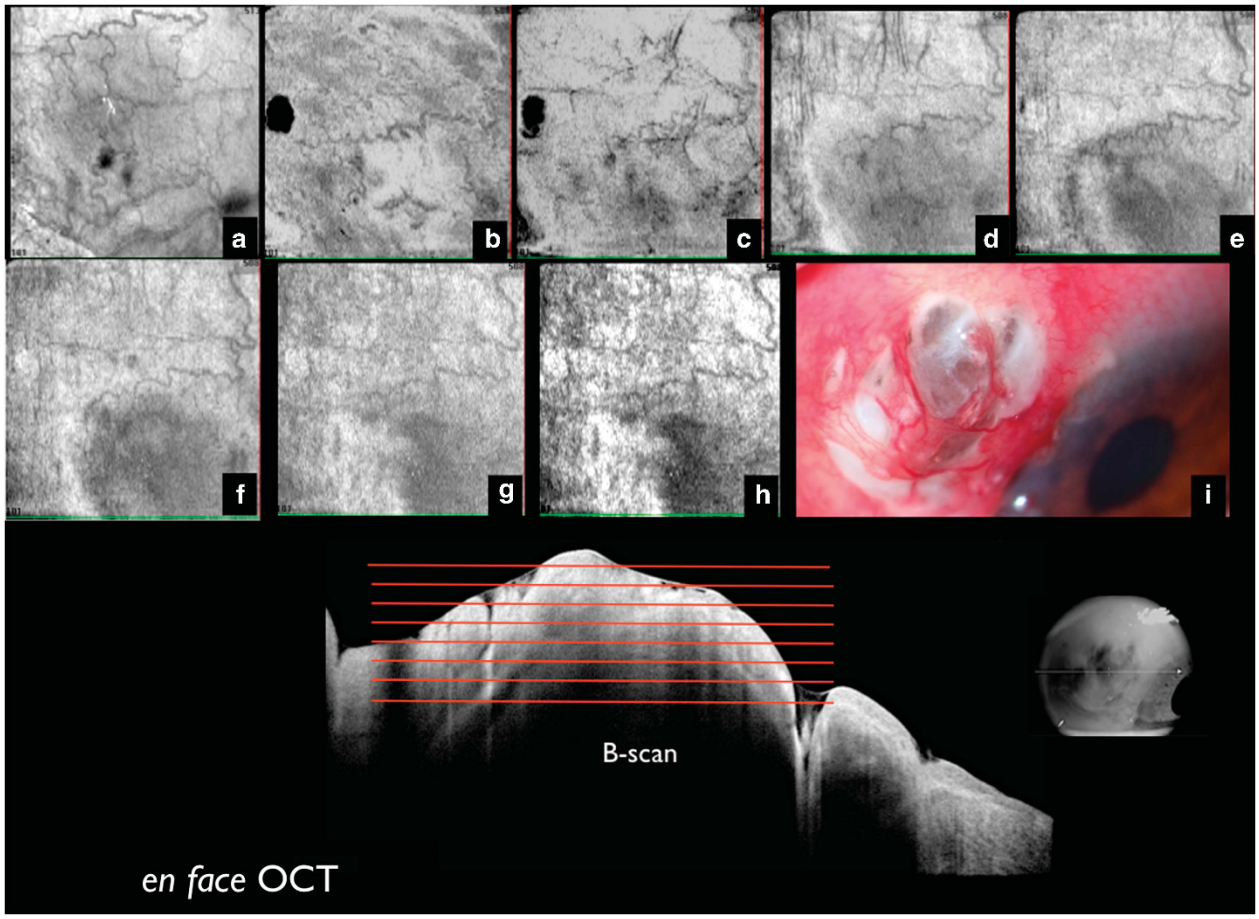

Figure 8 *En face* OCT in necrotizing scleritis. The depth, structure, and extent of the lesion can be determined. *En face* image integrated over the full-scan range of the sclera. Horizontal B-scan image through the centre of the scleral lesion in a patient with necrotizing scleritis (i) with overlay contour lines indicating the positions of partial intensity *en face* images. *En face* image of the 30 μm thick slab immediately underneath the conjunctival epithelium (a–h). A hyporeflective image indicates destruction of the posterior surface of the sclera (f–h).

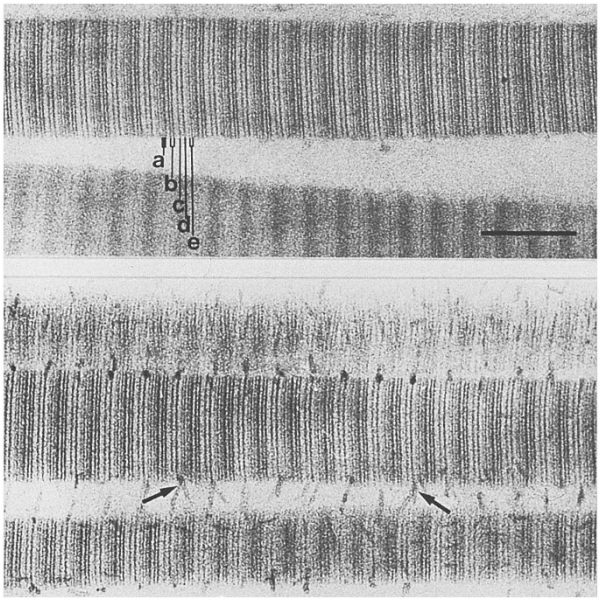

Figure 9 Scleral collagen and its associated proteoglycans. Scleral collagen fibrils exhibit a–e cross-banding in longitudinal sections (top panel). Cuprolinic blue staining visualizes proteglycans as filaments is associated with the d bands. These filaments lie along the fibril, encircle it, and connect the collagen fibrils to each other (lower panel).[18]

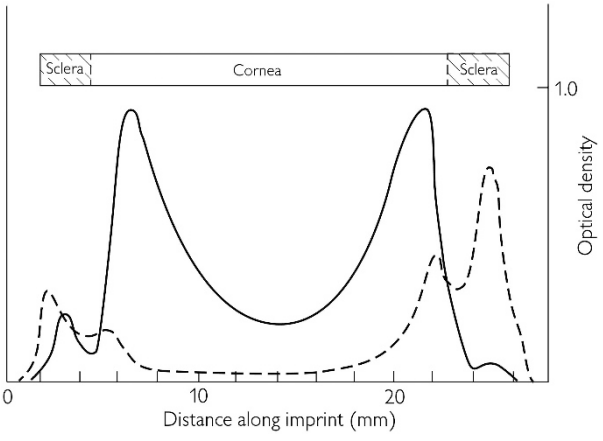

Figure 10 The distribution of immume proteins in cornea and sclera.[19]

and vasculitis, showed various forms of massive lymphocytic infiltration of the tissues and destructive changes in areas of cell death (Figure 11), and 12 of the 14 cases examined were found to have come from patients with an immune-mediated disease.[8]

Immunohistological changes

The immunohistological investigation of pathological specimens by Usui *et al*[10] show that the immunohistology of nonnecrotizing and necrotizing scleritis also differed (Figure 11). The cytokine profile of those with diffuse and nodular scleritis consisted of 43% CD68 macrophages, 23% CD3 cells, 5% CD8, 1% DRC, but only 7% CD20 B cells, highly suggestive of an autoimmune response. This was in sharp contrast to specimens from those with necrotizing scleritis where the profile was 43% CD20 B cells, 35% CD68 macrophages, 17% CD3, 8% CD8, and 4% DRC, indicating the presence of a systemic vasculitis. It has since been shown that those with an expanded CD8 (+) T-cell memory population have a poor prognosis.[11] The relatively large number of macrophages is also to be expected in this condition because of the presence of necrotic tissue.

What is it that initiates and perpetuates the immune response that leads to scleral inflammation? All the available evidence suggests that with the exception of those cases of infection, some unusual disorders of collagen such as the Ehlers Danlos syndrome and in episcleral disorders where there is localized vascular spasm, scleral and episcleral inflammation is immune mediated (see ref. 2 p 155, Figures 7.2, 7.3, 7.5).[6] What has not been clear is what is triggering the inflammatory response, what is the immune response driven against, and what causes the inflammation to persist. In addition, it has not been certain why, once the immune response has been triggered, the manifestations of the disease are so different in each individual. This is important because if these questions can be answered, therapy can be targeted at a particular response or even a subset of inflammatory cells.

In the nineteenth century, and presumably before this, the commonest cause of scleritis was tuberculosis. The inflammation was not the result of a primary invasion of the tissue by the tubercle bacillus but an immune response to it. As this disease was brought under control, the commonest cause then became rheumatoid arthritis. Now that rheumatoid arthritis can be treated early and more effectively, scleritis associated with this disease has become unusual and hence the commonest cause of necrotizing scleritis is now from the various manifestations of the systemic vasculitides. In countries where immune deficiency is common, syphilis and tuberculosis and the accompanying scleral complications are prevalent again. In places where leprosy is common, lepromatous leprosy should always be considered in the differential diagnosis as scleritis can be the first clinical manifestation of this disease.

How is it that the immune response is triggered by a variety of microorganisms resulting in a condition that appears to be identical clinically? The portal of entry of the infective organism or particulate matter is through the lung and, probably as in some bacteria, some virus infections and acanthamoeba, the conjunctiva. Occasionally, in Borellia

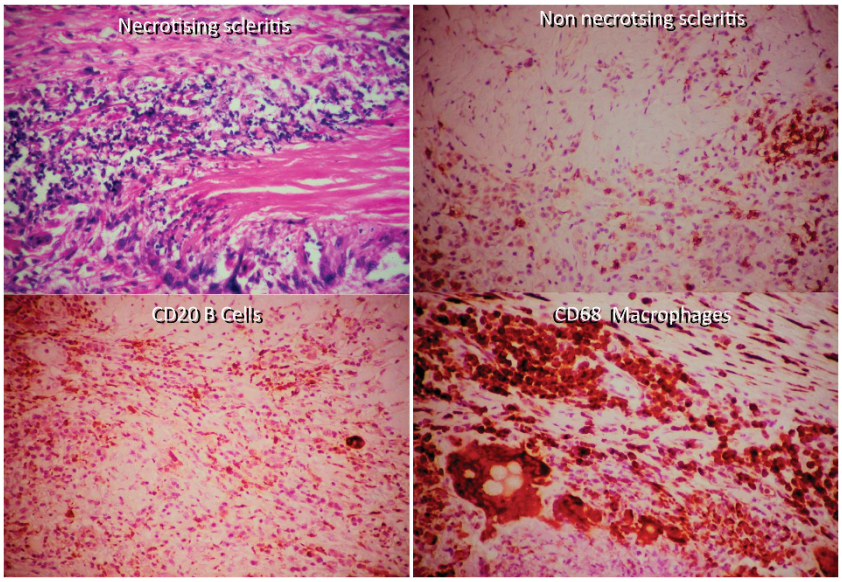

Figure 11 (Left above) Zonal necrotizing granulomatous inflammation in rheumatoid arthritis showing an acellular necrotic centre with an infiltration of inflammatory cells and some giant cells. (Left below) Staining for CD20 B cells in the same patient. (Right above) Scleritis in a patient with no evidence of systemic disease. There is diffuse infiltration of the sclera with inflammatory cells. (Right below) Staining for CD8 macrophages in the top right patient. The predominant cell is the macrophage (ref. 2 p 177, Figure 7.39).

infection or following trauma or surgery, the portal of entry is via the skin. Proteinases from these organisms are recognized by the microbial pattern recognition receptor (innate immune receptor), Toll-like receptor 4 (TL4) expressed on macrophages, and dendritic cells. The Toll receptor family, collectively referred to as pathogen-associated molecular patterns (PAMPs), associate with interleukin-1 to form a receptor superfamily. The immune system responds not only to these evolutionary conserved danger signals but also to damaged cells from the tissues themselves and from the immune system itself (danger associated molecular patterns (DAMPs).[12,13] Many bacterial molecules and DAMPS can activate TLR4 which may trigger a common signalling pathway resulting in similar histological changes. The foreign proteinases cleave the clotting protein fibrinogen.[14] The fibrinogen cleavage product then acts as a TLR4 ligand on epithelial cells, antigen-presenting cells, and macrophages, leading to inflammation. This discovery of the importance of fibrinogen cleavage in the allergic inflammatory process is the missing link that has been elusive for so long.

In the experiments of Millien *et al*,[14] they had to use ovalbumen challenge as they were investigating the fungal proteinases in asthma that does not occur naturally in rats and mice. It is of interest that the only animal model of scleritis to be produced was by ovalbumen challenge.[15] In this instance, the predominant features were the presences of T cells, macrophages and the activation of the fibrocytes by immune complexes.

Why does the inflammation occur in sclera, a tissue that is structural in nature and has no direct blood supply? Episcleritis has all the characteristics of a localized hypersensitivity response affecting only the superficial vascular plexuses with outpouring of fluid and cells in the affected area. It is less clear why the sclera, which derives its nutrition from branches of the anterior ciliary artery and the terminal vessels of the long posterior ciliary artery, should become involved in the inflammatory process.

Characteristically, inflammation of the sclera and its overlying episclera first appears in the upper inner or outer quadrants of the eye. The reason why scleritis starts in these regions between the extraocular muscles is that the superficial blood supply is unusual in that there is an artery to artery anastamosis between the terminal branches of the anterior ciliary arteries and between the terminal and perforating branches of the long posterior ciliary arteries. Although this arrangement ensures an adequate arterial blood supply to the anterior segment of the eye at all times, it has the consequence, at least in the superficial vasculature, that instead of a rapid flow of blood from the arterial to the venous circulation through a capillary network, the flow is sluggish, even oscillating. Thus, if immune-competent cells leave the arteriolar circulation in these areas, there is no immediate return to the venules, giving time for immune reactions to be triggered, enhanced, and perpetuated rather than being dealt with by the innate immune response as in tissues with a rapid circulation. Furthermore, if there is a

vasculitis of the terminal choroidal vessels, as can be seen in end-stage histological specimens (see ref. 2 p 155 Figures 7.2, 7.3, 7.5), the inflammation can extend through the sclera with the perforating vessels to the surface, where isolated vasculitic lesions are known to occur Figure 12. Hitherto it has not been suspected that the inflammatory process could start deep to the sclera rather than on the scleral surface and its overlying membranes (Figures 3 and 6–8).

How is it that diffuse and nodular scleritis have such a different course to necrotizing scleritis if their origin is the same? The immunohistochemical evidence suggests that, unlike necrotizing scleritis, diffuse and nonnecrotizing nodular disease are the result of an autoimmune process starting from within the sclera itself; its components responding to, or initiating, not only DAMP, activated circulating antigen-presenting cells, and macrophages, but also under certain circumstances resident macrophages. Resident tissue macrophages are present at birth and remain throughout life. Under certain circumstances, as in the induction of diffuse and nonnecrotizing nodular scleritis, they may assume an M1 inflammatory phenotype. The involvement of these resident macrophages could also explain why in SINS, when an area has been damaged remote from the current insult, as in a previous strabismus operation this becomes the site of the scleral inflammation.

The immunohistochemistry suggests that the sequence of events is different in necrotizing scleritis, a complication of an already present (if not always manifest) systemic immune-mediated systemic disease and its associated vasculitis. Scleritis can be the presenting feature of some of these (Figure 13), with its presence in or under the sclera being because of the sluggish circulations resulting from the unusual end artery and interarterial connections or part of a systemic multiorgan vasculitis.

Where the cytokine release is sufficient to cause activation of the scleral stromal fibrocytes, then destructive catabolic changes can take place. First, the protective activity of tissue inhibitor of metalloproteinases (TIMPs) (see ref. 2 p 158, Figures 7.10,7.11, 7.12 and pp 171-172, Figures 7.27, 7.28, 7.29) is reduced, allowing proteoglycan to be removed from the surface of the collagen fibril that then becomes unravelled and separated from its neighbour Figure 14. The exposure of the collagen, which has never before been exposed to the immune system, can either result in loss of tolerance or stimulate an inflammatory response, leading to antibody production, immune complex deposition, and the induction and perpetuation of the autoimmune response.

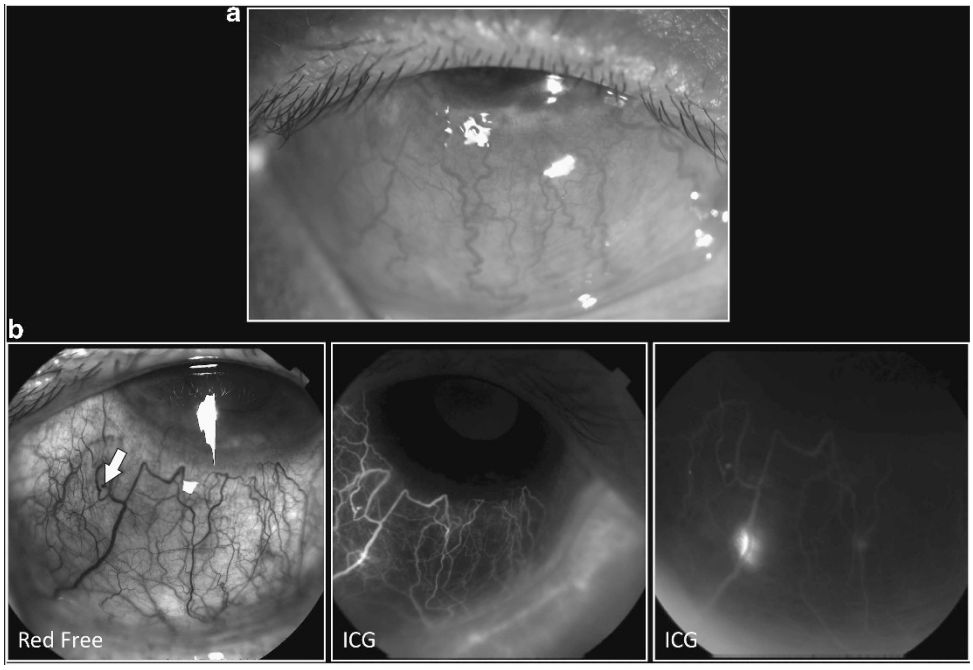

Figure 12 Granulomatous scleritis in granulomatosis with polyangiitis (Wegener's granulomatosis). (a) The characteristic presentation where the inflammation includes the limbus and adjacent cornea (in rheumatoid arthritis the limbal area is spared). (b) Red Free and ICG after 2 weeks of intensive treatment. The eye appears completely quiet on the red free but ICG reveals an intense staining at an area of vasculitis. Treatment should not be discontinued until these areas have healed.

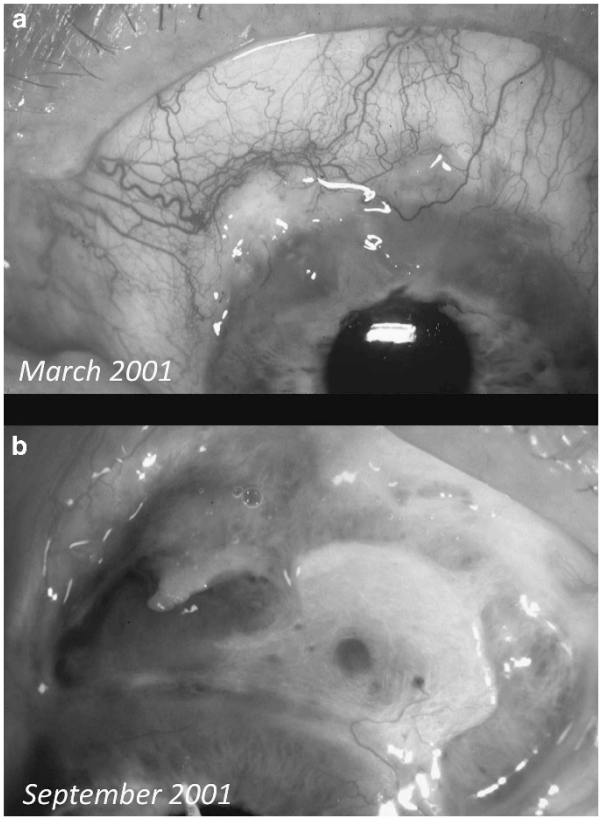

Figure 13 Necrotizing scleritis associated with granulomatosis with polyangiitis (Wegener's granulomatosis). A 57-year-old woman who presented with a red eye that was painful for 3 months. (a) The corneal destructive changes involve the whole limbus typical of that seen in a systemic vasculitis even though the ANCA was negative at this time. (b) After 17 months. Advice that she should be treated systemically was not accepted even though she had become ANCA positive by April 2001.

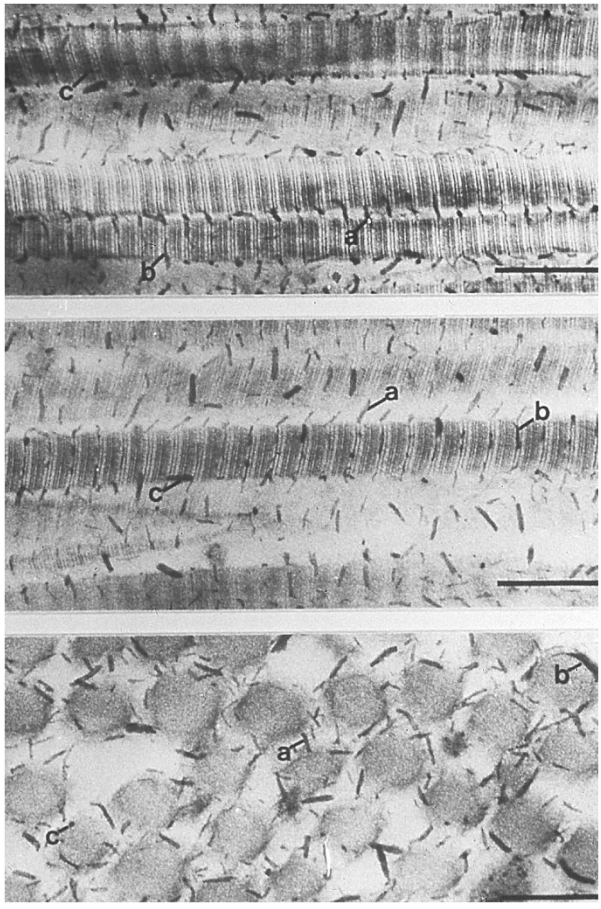

Figure 14 Normal collagen/proteoglycan structure on human sclera. In necrotising scleritis the proteoglycan separates from the collagen leading to unravelling of the collagen and its exposure to cytokine activity. (a) Proteoglycan fibrils connecting collagen to collagen. (b) Encircling proteoglycan fibril. (c) Proteoglycan fibril along the collagen (ref. 2 pp 158-159, Figures 7.10, 7.11, 7.12, 7.13).

Why should the cornea react in different ways in patients with apparently similar scleral disease? Anterior segment fluorescein/ICG angiography has helped to resolve the puzzle as to why the cornea reacts in different ways in different patients with apparently similar disease.

The corneal changes that are seen in association with scleral inflammation are of four types: Contact lens cornea, scleralization of the cornea, peripheral corneal destruction/guttering, and central corneal dissolution Figure 15.

Contact lens cornea

In contact lens cornea, the peripheral cornea becomes thinner and thinner without any obvious infiltration, coming to resemble a contact lens sitting on the cornea. Fluorescein/ICG angiography shows the adjacent limbal capillary network to be extensively attenuated, with a few new vessels passing into the peripheral superficial cornea. Nutrients for the maintenance of corneal collagen come from the limbus and by diffusion from the anterior chamber (Figure 10). The central cornea is maintained by the elution of nutrients through the central cornea, but the periphery is deprived of these because of the grossly reduced blood supply and, as a consequence, gradually diminishes in thickness (Figure 16).

Scleralization of the cornea

After prolonged or repeated attacks of scleral inflammation at the same site, the cornea begins to become opaque, the so-called scleralization of the cornea. In the early and acute phases of scleral inflammation, corneal infiltrates can be observed as an acute stromal keratitis, sometimes with immune rings around them, clearly the result of an antigen antibody response at that site. It is probably fair to assume that the same process is

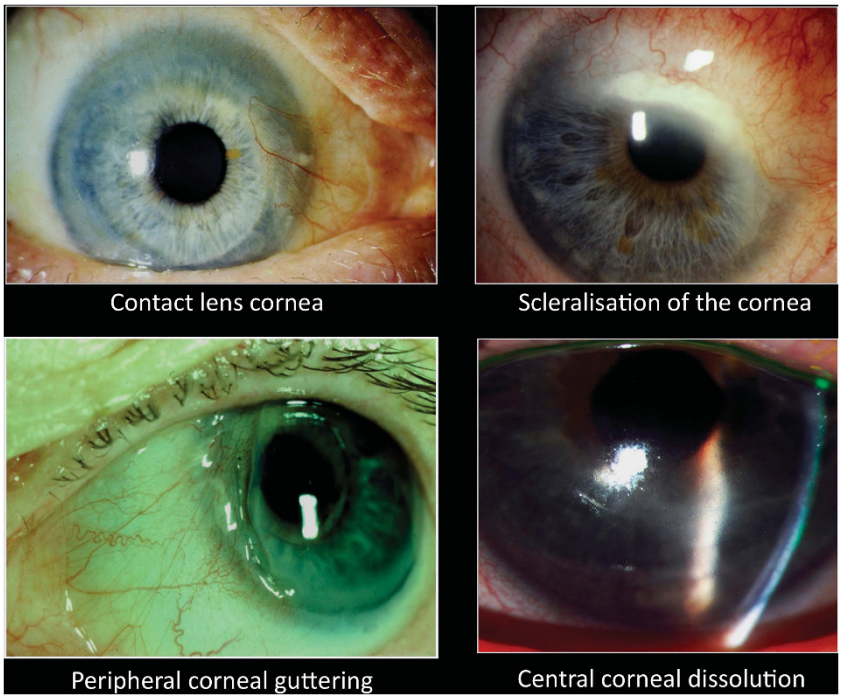

Figure 15 The corneal changes associated with scleral inflammation.

happening in the sclera at the same time. The opacification of the cornea is occasionally because of the persistence and extension of the precipitation of these immune complexes following an acute sclerokeratitis, but more often, as is shown by fluorescein/ICG angiography, the opacification is the result of destruction of the normal limbal arcade by the inflammation and the stem cells contained within them. If this happens, the conjunctiva and its vessels will overgrow the cornea, allowing opacification of the tissue beneath.

Peripheral corneal destruction

In the presence of scleral inflammation there can also be an infiltration and eventual loss of corneal tissue. In idiopathic and rheumatoid-associated sclerokeratitis, this peripheral change usually begins 2 mm inside the limbus with an inflammatory infiltrate that, if the inflammatory process is allowed to continue, results in a breakdown of the cornea stroma. In these individuals, even though there may be an associated necrotizing scleritis, the sclera immediately adjacent to the limbus appears to be entirely normal except for some abnormal vessels.

The site of destruction in both the sclera and cornea in peripheral corneal/guttering, 2 mm either side of the limbus, is the site of the highest concentration of immune proteins (Figure 10). The limbus, which is fed and drained by two different circulations, is spared because of the high concentration of blood vessels there.

In rheumatoid arthritis, the characteristic changes seen in this situation are those of a venular occlusive scleritis affecting the vessels of the episcleral plexus. Fluorescein/ICG angiography shows that the flow of blood within the capillary and arteriolar circulations of the networks is slowed; the vessels themselves becoming partially or completely occluded (see ref. 2 pp 158–159, Figures 7.14, 7.16, 7.17).

In contrast, the vascular changes associated with the corneoscleral pathology in a systemic, potentially fatal, vasculitis are quite different. These limbal changes may be the presenting feature of the systemic disorder, and hence it is important to recognize granulomatous scleritis as soon as it presents. In the presence of a systemic vasculitis, the destructive changes involve the cornea, limbus, and adjacent sclera equally; there is no area of apparently normal sclera adjacent to the limbus. All the tissues are involved together in the destructive process (Figures 12 and 13). This is the result of the vasculitis that affects blood vessels of all sizes. The limbal blood supply revealed when all the other tissues have been digested away is found to be enormous and is derived from all the those vessels feeding the anterior segment. Therefore, it is to be expected that the tissue of the limbus will be affected in an inflammatory vascular disease.

Fluorescein/ICG angiography reveals grossly abnormal vascular networks in the feeding vessels to the site of inflammation, including aneurysms and most importantly inflamed vessel walls Figure 12. Treatment must not be stopped before these inflamed areas have stopped leaking.

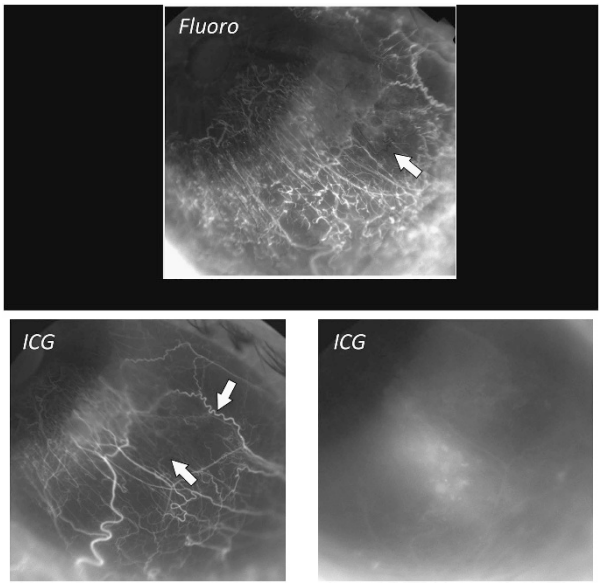

Figure 16 Contact lens cornea. Fluoresceine/ICG angiograms showing closure of the episleral capillary network associated with long-standing scleral inflammation. Fluorescein shows closure (arrow) with secondary overgrowth of the conjunctival vessels over the limbus to the edge of cornea of normal thickness. ICG images confirm the gross reduction of episcleral capillaries and leakage from the remaining ones (between arrows).

Central corneal dissolution

Very occasionally in patients with rheumatoid arthritis, the whole of the central corneal tissue will swell without obvious cellular infiltration. The cause of this rare but severe acute immune response is not known but is likely because of the presence of a 54 kDa antigen found in the cornea in this condition. Whatever the cause, if it is not treated in time the stroma will dissolve, leaving only the epithelium and Descemet's membrane intact.

How is it that the cornea becomes involved in scleral disease when the structure and constitution are so different? The macromolecular composition of the collagens and proteoglycans, its structural organization, and its fibrocytes of cornea and sclera are all different. These differences, which have been extensively investigated by Watson and Young,[5] reveal that the differences lie in the arrangement of both collagen and its proteoglycan coat.

With one or two notable exceptions unless the inflammatory response is very intense, the cornea is not usually involved in scleral disease. The corneal collagen network is regular in size and much more tightly bound together and will only break apart if there is a major influx of inflammatory cells as the result of intense adjacent inflammation (Figure 17). In addition, if the proposition is accepted that each specialized tissue is capable of recognizing and responding to its own danger signals, then corneal changes would not be expected.[12]

On the other hand, when the adaptive immune response has been triggered and the sclera becomes involved the proteoglycan bonds between the collagen, fibrils break apart (see ref. 2 p 158, Figures 7.10, 7.11, 7.12). In nonnecrotizing scleritis they may be restored by remodelling if treatment is successful, but in necrotizing scleritis the proteoglycans surrounding the collagen fibrils may be permanently lost, exposing the fibrils to prolonged enzymic attack, causing them to unravel. This may reveal collagen neoepitopes never previously exposed to the immune system that subsequently act as an antigen inducing a further inflammatory response.

How does the perceived difference between nonnecrotizing disease and its more serious counterpart affect treatment? Before 1950, the only treatment that could be offered to anyone with scleral inflammation was palliative. It consisted of atropine eye drops, aspirin, or morphine derivatives for the pain, and bathing of the eye with either warm or cold compresses that gave some form of counter irritant and temporary comfort. As the common cause at that time was tuberculosis, the equally ineffective treatments for this condition were often added on top. If patients recovered, it was because of their underlying good constitution and the superb nursing of the patients of that time rather than the intervention of the physician. The introduction of locally applied steroid eye drops in the 1950s not only led to a dramatic improvement in the comfort of the patients but also to regression of the signs and symptoms. The use of nonsteroidal anti-inflammatory agents (NSAIDs) other than aspirin and the use of high-dose and pulsed steroid was the major advance of the 1960s. Because these regimes suppressed the inflammation, the progression of the disease was stopped and, if the sclera had been damaged, allowed healing to take place. The other important revelation of this treatment was that it showed that scleral inflammation was the result of an immunological process and rarely the result of direct infection that had been assumed in the past. The next three decades have been spent elucidating the cells that induced the destructive process and their effect on the connective tissue and other components of the sclera and its coats.

Steroids, effective as they may be, have the effect of a blunderbuss; undirected, widely effective but not directed at a particular target. Oral steroids affect many parts of the inflammatory pathway but do not target any specific aspect of it and, in addition, have multiple undesirable side effects. However, subconjunctival triamcinalone has been shown to be effective in reducing these to a minimum in nonnecrotizing scleritis. As it has

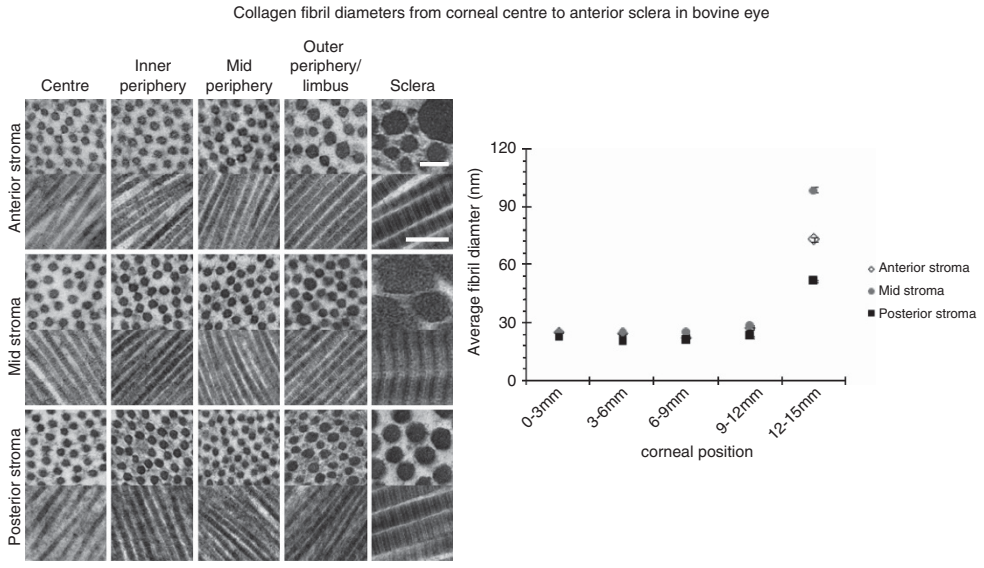

Figure 17 Cross-sectional and longitudinal TEM micrographs of collagen fibrils across the bovine cornea and sclera. The collagen fibril diameter is uniform from the cornea centre until the limbus where it varies to increase significantly into the sclera. This is so in the outer mid and deep stroma. Scale bar = 100 nm (cross-sectional) and 200 nm (longitudinal). The mean fibril diameter across the bovine cornea and sclera is shown in the graph. 0–3 nm = centre; 3–6 nm = inner perphery; 6–9 = mid periphery, 9–12 = outer periphery; and 12–15 = sclera (Ho *et al*, submitted).

been shown that there is no overlap in the manifestations of nonnecrotizing scleritis and the conditions that lead to tissue destruction (Table 2), it follows that although remission can be induced in diffuse and nodular scleritis with NSAIDs, subconjunctival triamcinalole, or a short course of steroids, necrotizing disease needs to be treated from the outset with systemic immunosuppression and disease-modifying agents such as methotrexate. It has become recognized that TNF-α is involved in most of the important parts of the inflammatory pathway and that monoclonal antibodies to this substance are effective in reducing the number and amount of inflammatory cells of all classes, thus inhibiting the intense destructive process and allowing healing to take place. The compounds in common use are infliximab, adalimumab, and rituximab. It has been found that rituximab, known to be most effective against B cells (associated with vasculitis), is much more effective in the treatment of scleral disease than infliximab.

The management of scleral disease in the future

It is sometimes questioned why pioneers in ophthalmology such as Jules Francois, von Graefe, MacKenzie, Gonin, and my old mentor Sir Stewart Duke Elder should be commemorated. It is because these were the people who above all brought together all the available knowledge of the eye and its diseases in their era and hence allowed great leaps forward in the diagnosis and treatment of the diseases that they brought to everyone's attention.

Jules Francois' pioneering work and classic text on genetically determined diseases of the eye has led to the identification of those conditions that are possibly amenable to the first successful stem cell implant treatments in medicine.

These individuals marked the end of the era when description of disease was all that could be done. The succeeding decades have taken this knowledge and have found ways, with the help of technology and pharmacy, of dealing with most of the problems, reducing dramatically the level of blindness worldwide.

Within the past 3 or 4 years, we have entered a new revolutionary period that, I believe, will change the way not only ophthalmology but the whole of medicine is taught and practiced. This is the smart phone revolution. Expert help in the diagnosis and treatment in unusual conditions such as scleritis will be available to all in however remote a community. Attachments to a smart phone can measure visual acuity, do accurate visual fields, measure intraocular pressure, refract, take accurate high-quality images of corneal external diseases, and excellent fundus photographs. Furthermore, the PEEK project in Kenya has shown that these investigations can be undertaken by health-care workers who have had only a few hours of training (Figures 18 and 19).

As smart phones are now ubiquitous organized, or even self, assessment is becoming widespread and not

Table 2 The differences between necrotizing and nonnecrotizing scleritis, its investigations, its pathology, and the course of the disorder from its presentation

	Necrotizing scleritis	*Diffuse, nodular scleritis*
Presentation	Severe pain, intense Intense inflammation	Gradual onset, moderate pain Diffuse or nodular presentation
Course	Unremitting	Recurrent or self-healing
Identity	No change throughout	No change throughout
Trigger	Trauma, infection	Rarely determined, stress
Systemic disease	Common, RA, vasculitis	Uncommon
Area of scleritis	Anterior	Anterior and posterior
Cornea	Often involved	Rarely involved
Angiography	Disturbed vascular pattern from onset, vasculitis	Vascular pattern only altered in chronic or recurrent disease
OCT	Destruction and aggregation of collagen fibrils superficial and deep to sclera	Separation of collagen fibrils oedema, with cellular infiltrates
Histology	Granulomatous, vasculitis fibrinoid necrosis adjacent to vessels. Central necrosis histiocytes, lymphocytes close to necrosis, plasma cells lymphocytes surrounding zonal necrosis	Diffuse inflammation of episcleral and scleral tissue lymphocytic infiltrates, nongranulomatous
Immunopathology	43% CD20 B cells, 35% CD68 macrophage, and 8% CD8, indicating the presence of a systemic vasculitis	43% CD68 macrophage but only 7% CD20 B cells, highly suggestive of an autoimmune response
Complications	Glaucoma uveitis frequent	Rare except posterior scleritis
Treatment	Active immunosuppression required. Retuximab most effective	Moderate inflammation NSAID or steroid even spontaneous remission

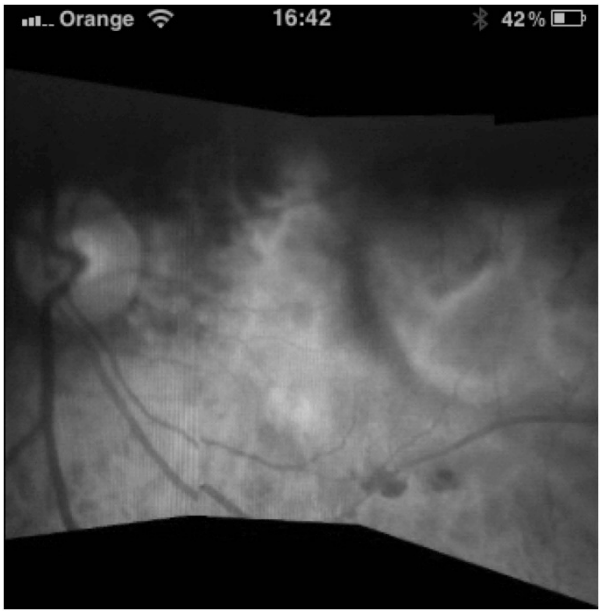

Figure 18 The 'stitched' composite fundus photgraph taken with an attachment to a smart phone of an exudative retinal detachment and retinal haemorrhages taken by a health-care worker in the PEEK project in Kenya ready to be transmitted to a diagnostic centre.

confined to Africa, India, and Asia. It means that ophthalmologists everywhere will have to become either surgeons, specialists in some particular condition, or expert advisors on where and how a patient should be treated. Everything else will be done by ancillary staff. Ophthalmologists may well find themselves treating conditions remotely, perhaps without ever seeing the patient. Training of budding medical students and ophthalmologists will have to reflect these changes. Times change and the loss of personal contact with the patient is going to be a real problem. Technology is king at the moment but, for me, it is good to have practised in an era where one saw everyone face to face and could ensure they left you with a smile on their face however grim the diagnosis.

Conclusions

Analysis of the presentation and the course of noninfective scleritis together with the additional evidence derived from deep anterior segment OCT/*en face* OCT, fluorescein/ICG imaging, histology, and the immunohistochemical investigations confirms that the original classification of scleral disease has stood the test of time and is still correct.

The new algorithms for anterior segment OCT imaging indicate that there are two forms of nodular scleritis: one in which the collagen fibres are simply separated as in the nonnecrotizing forms of scleritis and the other where the contents liquefy in a similar manner to the destructive changes of necrotizing scleritis.

In addition, the increased ability to observe the deeper layers of the sclera with this technique suggests that scleritis is associated with changes within the potential suprachoroidal space, deep to the sclera as well as superficial to it. This observation is

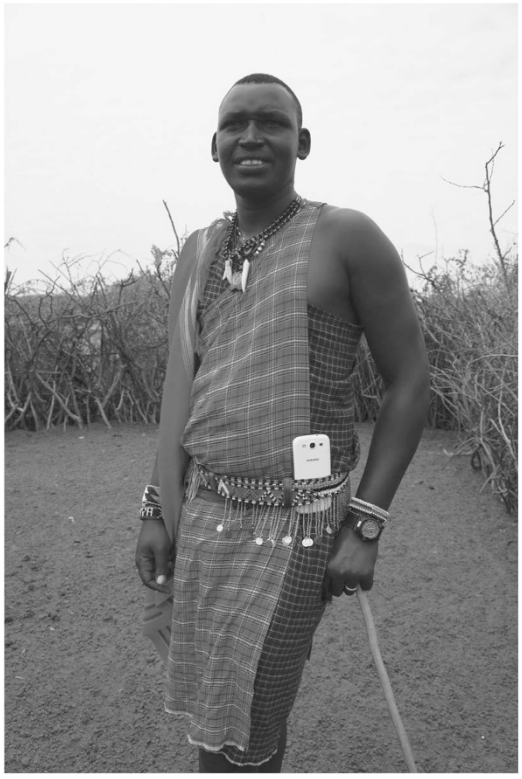

Figure 19 Masai health-care worker in PEEK project. He has two watches and his diagnostic smart phone in his belt.

endorsed by the study of end-stage pathological specimens that reveal the presence of subscleral granulomas. If the choroid becomes involved in an intense inflammatory response, an exudative detachment will occur.

Analysis of the clinical progress of scleritis and studies of the immunohistology indicates that necrotizing scleritis and diffuse and nodular scleritis pursue a different course not only in their clinical manifestations but also in their pathogenesis. From the initiation of the inflammatory process, the manifestations of the disease rarely, if ever, change throughout their clinical course (Table 2).

These studies suggest that nonnecrotizing disease is an autoimmune process starting from within the structural contents of the sclera. The inflammation, which is largely driven by the innate immune system, responds not only to DAMP-activated circulating antigen-presenting cells and macrophages and granulocytes but also resident tissue macrophages.

The immunohistology of necrotizing scleritis, on the other hand, shows a predominance of B cells and a high concentration of macrophages that will induce changes in the stromal environment[16] and activate acquired immunity so that the scleritis becomes the consequence of the vasculitis accompanying an already present (if not always manifest) systemic immune-mediated systemic disease. Scleritis can be the presenting feature of some of these. The genetic constitution may affect the course of the condition; for instance, patients having the HLA-DRB1 phenotype are more likely to develop this complication.[6]

The reason why the sclera is possibly more susceptible to an inflammatory reaction than other tissues is that the vascular circulations around the sclera are unique in that both the superficial and deep choroidal arteries are end arteries. Although there are major anastamoses that guarantee a continuous circulation to the front of the eye, the anastamoses superficially are between arteries and hence the arterial circulation is sluggish or even oscillating, leaving time for immune reactions to take place.[17]

The implication of these conclusions is that the investigation of diffuse and nodular scleritis should be restricted to eliminating the possibility of the development of necrotizing disease where the clinical signs are equivocal. Investigations of necrotizing disease need to be directed at finding the underlying systemic disease. This is particularly important in systemic vasculitis where scleritis may be the presenting feature.

The other obvious implication is that whereas nonnecrotizing scleritis only needs limited medication for its treatment, necrotizing scleritis must be treated with intense immunosuppression from the time of diagnosis.

Conflict of interest

Peter Watson declares no conflict of interest. Andre Romano is a consultant for Optovue, Inc. and has received research support from them.

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