Episcleritis and scleritis

A study of their clinical manifestations and association with rheumatoid arthritis

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Sir William Read, Royal Ophthalmologist during the reign of Queen Anne (1702–1714), who incidentally was unable to read or write (Guthrie, 1958), gave a choice description of the dangers of perforation in deep scleritis: 'For it is most certain that this horny membrane . . . by how much deeper the blister is hidden in the membrane . . . in danger to make an ulceration by breaking through the membrane, whereupon may ensue an utter loss and decay of all the humours'. Further documentation of the sequelae of scleral inflammation awaited a further century for the description of staphylomata by Scarpa (1818), who described two cases of posterior staphylomata found at necropsy. Mackenzie (1830) attributed scleritis to atmospheric conditions and suggested the term 'sclerotitis atmospherica' or 'rheumatic ophthalmia'. Later Mackenzie (1854) was to suggest the name 'sclerotitis idiopathica'. Wolfe (1882), lecturing to the students of Anderson College, Glasgow, used the currently accepted nomenclature of episcleritis and scleritis. The later terminology has been excellently recorded by Sevel (1967).

Earlier authors often associated inflammation of the sclera with rheumatic disease (Mackenzie, 1830; Littell, 1840; Wolfe, 1882; von Arlt, 1885). Besides 'rheumatism', scleritis was attributed to gout (Cleobury, 1826; Walton, 1875), mercury poisoning (Morgan, 1839), venereal disease, particularly syphilis (Morgan, 1839; von Arlt, 1885); scrofula (Mackenzie, 1854); excessive exposure to varying atmospheric conditions (Mackenzie, 1830; de Schweinitz, 1899), and menstrual derangement (de Schweinitz, 1899).

The most consistent systemic disorder associated with episcleritis and scleritis, particularly the latter, is rheumatoid arthritis (Van der Hoeve, 1934; Verhoeff and King, 1938; Smoleroff, 1943; Edstrom and Osterlind, 1948; Mundy, Howard, Stillman, and Bevans, 1951; Hollenhorst and Henderson, 1951; Watson and Lobascher, 1965; Watson, 1966; Lyne and Pitkeathly, 1968; Fowler, 1970;

Jayson and Jones, 1971), and with this in mind the present study differentiates rheumatoid episcleritis and scleritis from non-rheumatoid episcleritis and scleritis according to the criteria for 'classical' or 'definite' rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959).

Material and methods

Examination of patients was carried out at two centres: the Centre for Rheumatic Diseases, Glasgow, and the Tennent Institute of Ophthalmology, Western Infirmary, Glasgow.

During the years 1965 to 1973 any patient seen at the Centre for Rheumatic Diseases with rheumatoid arthritis who had any eye complaint was referred to an ophthalmologist and any case of episcleritis or scleritis was examined in detail. Those patients examined before 1971 who were still alive were recalled to hospital or visited in their homes. It was at the beginning of 1971 that a scleritis clinic was instituted at the Tennent Institute, and a pro forma outlined the investigations to be documented for patients at both centres. In all patients these investigations included examination by an ophthalmologist and by a rheumatologist; this was supplemented by laboratory investigations appropriate to ocular inflammation and rheumatoid disease.

The purpose of the study was to compare patients who presented with rheumatoid disease, who subsequently developed episcleritis and scleritis, with patients who presented with episcleritis or scleritis in whom rheumatoid disease was incidental to their referral.

CENTRE FOR RHEUMATIC DISEASES

Between 1965 and 1973, 4210 patients with rheumatoid arthritis were examined at the Centre for Rheumatic Diseases. These patients satisfied the diagnostic criteria of the American Rheumatism Association (Ropes and others, 1959). Seven of these patients had episcleritis and 28 had scleritis.

TENNENT INSTITUTE OF OPHTHALMOLOGY

During 1971 and 1972, 62 patients were examined at the scleritis clinic: 35 of these patients had episcleritis and 27 had scleritis. Two of the patients with episcleritis and nine of the patients with scleritis had rheumatoid

arthritis according to the criteria already cited (Ropes and others, 1959).

The presentation of results initially gives the incidence of episcleritis and scleritis in rheumatoid arthritis, and also the incidence of rheumatoid arthritis in episcleritis and scleritis. Thereafter, unless it is otherwise indicated, the patients are divided into those with rheumatoid disease and those without rheumatoid disease. This results in four groups of patients with:

1. Rheumatoid episcleritis (nine cases)
2. Rheumatoid scleritis (37 cases)
3. Non-rheumatoid episcleritis (33 cases)
4. Non-rheumatoid scleritis (18 cases)

Comparisons are made between these four groups of patients. In the section dealing with the systemic manifestations of rheumatoid disease and also in some of the laboratory investigations a further comparison is made, that is, between the combined groups of rheumatoid episcleritis and scleritis and a group of rheumatoid controls, patients with rheumatoid arthritis matched for age and sex with the rheumatoid episcleritis/scleritis groups but without episcleral or scleral inflammation. This gives two further groups:

5. Rheumatoid episcleritis/scleritis (46 cases)
6. Rheumatoid controls (46 cases)

Statistical analysis is presented throughout the study. However, the numbers, in what is a relatively uncommon type of ocular inflammation, are often very limited. The biological meaning of statistical evidence therefore requires critical appraisal.

OPHTHALMIC EXAMINATION

Complaints of eye symptoms were elicited with as little prompting as possible. The duration of the condition was estimated from the first episode of inflammation. Accurate documentation of duration is difficult as it is not always certain that a condition which may persist intermittently during a period of some years has truly settled. Visual acuity was assessed by Snellen's test chart at the Tennent Institute with or without glasses as appropriate. Refraction was not done routinely.

The anterior segment of each eye was examined in diffuse light, often in ordinary daylight, and by detailed examination with a slit-lamp microscope. Patients seen in their homes were examined with a single loupe and focal light. Slit-lamp examination served to reveal the depth of inflammation, determining which network of vessels was predominantly affected. It is occasionally difficult to be certain whether an apparently nodular episcleritis is in fact a scleritis; the diagnosis is often more readily apparent in retrospect when, for example, an area of scleral translucency will indicate a scleritis. The greyish-blue colour of deep scleritis is due to the dark uvea becoming evident through translucent sclera. In contrast, episcleritis is usually bright red in colour. A careful slit-lamp examination after observation in diffuse light, with a conclusive diagnosis made only after observing the inflammation for varying periods of time, is sufficient in most cases to provide a diagnosis. Nevertheless, there remain a few cases in which it is impossible to differentiate with certainty an episcleritis from a superficial scleritis. The figures that are given, therefore, are not absolute, but the features associated with

predominantly superficial inflammation affecting primarily the episclera will be contrasted with features of deeper involvement affecting primarily the sclera.

Ophthalmic examination took note of any corneal complications, anterior uveitis and cataract, particularly posterior subcapsular cataract. The fundi were examined after instillation of cyclopentolate hydrochloride BP 1 per cent. A Haag-Streit applanation tonometer recorded the intraocular pressure in patients seen in hospital, and a Perkins hand-held applanation tonometer was used for those patients who were visited in their homes.

Any suggestion of limitation of extraocular muscle movement or history of diplopia prompted referral to the orthoptist for a more exact record.

All patients were screened for evidence of keratoconjunctivitis sicca (KCS) by Schirmer's tear test (Schirmer I) using standardized filter-paper strips*. The length of wetting of the filter paper at the end of 5 minutes was measured. A normal tear secretion was accepted as 15 mm wetting or more for patients under the age of 40 years, and 10 mm wetting for patients over the age of 40 years, as standardized by Halberg and Berens (1967). All patients with reduced tear flow had a drop of rose bengal 1 per cent instilled into the eye, and punctate staining indicated the presence of dead or dying cells and excess mucus. Confirmation of KCS was given by Schirmer's test (Schirmer II) in which a 10 per cent ammonia solution is held approximately 15.2 cm below the nose to stimulate tear production, which is recorded as in Schirmer I.

GENERAL EXAMINATION

The following investigations were designed to measure the severity of any disease of the locomotor system, and complications of rheumatoid arthritis and other connective-tissue disorders.

For each patient were recorded four grades of functional incapacity (Steinbrocker, Traeger, and Batterman, 1949). The articular index, a summation index, estimated the number of involved joints and the severity of their involvement as judged by tenderness to pressure over the joint margin. Radiological evidence of the degree of bone involvement was categorized in four stages of increasing severity (Steinbrocker and others, 1949).

A number of extra-articular complications of rheumatoid disease were noted: subcutaneous granulomatous nodules, peripheral neuropathy, vasculitis manifest as skin ulceration or bruising, and tendon rupture. Atrophy of skin was recorded as a recognized side-effect of treatment with systemic corticosteroids (Scarborough and Shuster, 1960; Greenwood, 1966). An enlarged spleen suggested the possibility of Felty's syndrome (Felty, 1924), and evidence of amyloidosis was noted, as rheumatoid arthritis is now the commonest cause of secondary amyloidosis in western countries (Boyle and Buchanan, 1971).

Xerostomia and salivary gland enlargement were recorded as features associated with Sjögren's syndrome (Sjögren, 1933).

*Developed by Halberg and Berens (Crookes-Barnes Laboratories, Inc., Wayne, NJ, USA)

An electrocardiogram was used in most patients (unless bedridden and visited at home) to exclude cardiac disease, which has been noted as a complication in patients with scleritis and rheumatoid arthritis (Smoleroff, 1943; Jayson and Jones, 1971). Blood pressure recordings and cardiac auscultation screened patients for aortic incompetence, which has been associated with scleritis (Pitkeathly, Howitt, and Lyne, 1970).

All patients had a chest x-ray examination to exclude evidence of active tuberculosis or sarcoidosis and to demonstrate any pulmonary complication of rheumatoid arthritis.

LABORATORY METHODS

In each patient the haemoglobin concentration, erythrocyte sedimentation rate, and serum proteins, although nonspecific in nature, reflected the severity of disease. Haemoglobin estimation at the Tennent Institute of Ophthalmology was given as a percentage, but in the Centre for Rheumatic Diseases it was given in grams per 100 ml. For comparison of data each haemoglobin value in g/100 ml was converted to a percentage reading, taking 14 g/100 ml as a value of 100 per cent. Alkaline phosphatase, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase were recorded to assess any association of liver disease and scleritis. Liver disease has been noted in 6 per cent of patients with Sjögren's syndrome without rheumatoid arthritis and in 1.5 per cent of patients with Sjögren's syndrome and rheumatoid arthritis (Whaley, Williamson, Dick, Goudie, Nuki, and Buchanan, 1970). Serum uric acid levels were estimated to exclude gout. In view of the relevance of scleritis in venereal disease, usually syphilis (Cleobury, 1826; von Arlt, 1885; Holloway and Fry, 1931), the Wassermann reaction, Venereal Disease Reference Laboratory (VDRL) slide test and Reiter protein complement-fixation test (RPCFT) were performed. Further investigations included the antistreptolysin-O titre, and tests for evidence of brucellosis and toxoplasmosis. The antistreptolysin-O titre may be raised in erythema nodosum, a condition associated with episcleritis (McCarthy, 1961). Brucellosis, a well recognized cause of uveitis (Woods and Guyton, 1944; Hewson, 1964), has been incriminated in a case of scleritis (Thomas, Helluy, Cordier, and Algan, 1953) and to exclude it the complement-fixation, standard agglutination (direct), and antihuman globulin (Coombs') tests were performed. Cat, Marinoni, Giralidi, and Costa (1971) reported that two of their cases of juvenile rheumatoid arthritis had high false positive titres for toxoplasmosis, and accordingly the toxoplasma dye test (Sabin and Feldman, 1948) was routinely investigated.

A multiplicity of autoantibodies may occur in the connective-tissue (collagen) disorders (Copeman, 1964). Scleritis has been called a collagen disorder (Hayreh and Watson, 1970). In view of this, autoantibody screening tests were undertaken in each case. Tests were carried out for rheumatoid factor, using the latex agglutination technique (Hyland Laboratories) (Ziff, Brown, Lospalluto, Badin, and McEwan, 1956), the R_3 latex agglutination test (Denver Laboratories) using

sera giving a positive result in the rheumatoid latex test, and by the tanned red-cell haemagglutination technique for thyroglobulin antibody (Fulthorpe, Roitt, Doniach, and Couchman, 1961). All the remaining autoantibody investigations applied the indirect immunofluorescent technique. These were tests for thyroid microsomal antibody, antinuclear factor, salivary duct antibody, mitochondrial antibody, gastric parietal-cell antibody, and smooth-muscle antibody (Table I).

The assay of complement C₃ (1c/1a globulin) used specific immunodiffusion plates (Hyland Laboratories) and serum concentrations of IgG, IgA, and IgM globulins were similarly measured by radial immunodiffusion using commercially-prepared plates (Behringwerke) according to the method of Mancini, Carbonara, and Heremans (1965).

EYE SWABS

Platinum loop scrapings and swabs taken from the conjunctiva of the inflamed eye (the more inflamed in bilateral disease) in each case seen at the Tennent Institute of Ophthalmology were sent for investigation of bacteria, fungi, and viruses. Platinum-loop scrapings were plated on chocolate agar for bacteriology. Isolation of fungi was effected by platinum-loop scrapings plated on 2 or 3 per cent malt extract agar with chloromycetin 0.05 mg/ml. Swabs for virus studies were placed immediately in Eagle's tryptose phosphate medium with calf serum 10 per cent.

TYPE I ALLERGY (ATOPY)

Lyne and Pitkeathly (1968) with J. W. Kerr and J. M. MacLeod noted that, in 25 of 33 cases having single attacks of episcleritis, the inflammation affected the interpalpebral area. The findings in this present study endorse their report and it seemed worth considering external aggravating factors in the category of immediate hypersensitivity. Altogether 23 patients, all of them with non-rheumatoid inflammation, and all except six cases of episcleritis, were subjected to skin testing for house dust, grass pollen, alternaria, feathers, house dust mite, *Aspergillus*, *Candida albicans*; and cat and dog hair, if one of these pets was in the home.

Table I *Autoantibody investigations*

<i>Autoantibody</i>	<i>Tissue substrate</i>	<i>Reference</i>
Thyroid microsomal	Human toxic thyroid	Holborow, Brown, Roitt, and Doniach (1959)
Antinuclear factor	Rat liver	Beck (1961)
Salivary duct	Human salivary gland	MacSween, Goudie, Anderson, Armstrong, Murray, Mason, Jasani, Boyle, Buchanan, and Williamson (1967)
Mitochondrial	Rat kidney	Goudie, MacSween, and Goldberg (1966)
Gastric parietal	Human gastric mucosa	Adams, Glen, Kennedy, McKenzie, Morrow, Anderson, Gray, and Middleton (1964)
Smooth muscle	Rat stomach smooth muscle	Johnson, Holborow, and Glynn (1965)

MORTALITY

An initial impression suggested that more of the patients with rheumatoid episcleritis or scleritis had died since examination as compared with the group of rheumatoid controls. The control group was carefully matched for age, sex, and year of presentation at the Centre for Rheumatic Diseases. Contact with the general practitioner of each patient determined which patients had died by February 1974. The Registrar of Births, Deaths and Marriages, Glasgow, provided information as to the cause of death in each case.

Results

INCIDENCE (Table II)

Between 1965 and 1973, 4210 patients with rheumatoid arthritis were examined at the Centre for Rheumatic Diseases. Seven of these patients had

Table II Incidence of episcleritis and scleritis in rheumatoid arthritis

Clinic	Disease	Cases	No. of patients with rheumatoid arthritis	Per-centage
Centre for Rheumatic Diseases 1965-73	Episcleritis	7	4210	0.17
	Scleritis	28	4210	0.67
Scleritis Clinic, Tennent Institute of Ophthalmology 1970-71	Episcleritis	35	2	5.7
	Scleritis	27	9	33.3

episcleritis (0.17 per cent) and 28 patients had scleritis (0.67 per cent).

Thirty-five cases of episcleritis and 27 cases of scleritis presented at the Tennent Institute of Ophthalmology during 1971 and 1972. Two of the cases of episcleritis (5.7 per cent) and nine of the cases with scleritis (33.3 per cent) had clinical and radiological evidence of rheumatoid arthritis according to the diagnostic criteria of the American Rheumatism Association (Ropes and others, 1959). Each of these cases was sero-positive for rheumatoid factor. One further case of episcleritis and six further cases of scleritis were weakly sero-positive for rheumatoid factor, but had no clinical or radiological evidence of rheumatoid arthritis.

(Unless otherwise indicated in the remaining data patients from both clinics with rheumatoid arthritis are combined and compared with the findings of patients without rheumatoid arthritis.)

AGE, SEX, AND BILATERALITY (Tables IIIa-f)

The only group of patients with a mean age outside the sixth decade was the non-rheumatoid episcleritis group which had a mean value of 45.1 years.

All cases with rheumatoid episcleritis were female and this was consistent with the higher incidence of rheumatoid arthritis in women. Scleritis was found in twice as many women as men (67.6 to 32.4 per cent). It is interesting to note that of the non-rheumatoid patients, episcleritis was found equally in women and men (48.5 and 51.5 per cent), but scleritis showed a marked preponderance in women (83.3 to 16.7 per cent).

The 9 patients with rheumatoid episcleritis

Table IIIa Age (rheumatoid episcleritis and rheumatoid scleritis) 46 cases

Disease	Cases	Age range (years)	Mean (years)	SD	SEM
Episcleritis	9	54-69	58.7	±5.9	±2.0
Scleritis	37	28-77	58.3	±11.8	±1.9

Statistical analysis: $t=0.0840$; $P=NS$

Table IIIb Age (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Disease	Cases	Age range (years)	Mean (years)	SD	SEM
Episcleritis	33	20-71	45.1	±14.6	±2.5
Scleritis	18	32-75	53.2	±13.7	±3.2

Statistical analysis: $t=1.8746$; $P=NS$

Statistical analysis (rheumatoid versus non-rheumatoid):

Episcleritis: $t=2.7092$; $P<0.005$

Scleritis: $t=1.5044$; $P=NS$

Table IIIc Sex ratio (rheumatoid episcleritis and rheumatoid scleritis) 46 cases

Disease	Cases	Females		Males		Ratio
		No.	Per cent	No.	Per cent	
Episcleritis	9	9	100	0	—	—
Scleritis	37	25	67.6	12	32.4	2.1/1
		34	73.9	12	26.1	2.8/1

Table IIId Sex ratio (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Disease	Cases	Females		Males		Ratio
		No.	Per cent	No.	Per cent	
Episcleritis	33	16	48.5	17	51.5	1/1.1
Scleritis	18	15	83.3	3	16.7	5/1
		31	60.8	20	39.2	1.6/1

Statistical analysis (female): $\chi^2=5.9337$; $P<0.02$

Statistical analysis (rheumatoid versus non-rheumatoid (female):

Scleritis: $t=1.5175$; $P=NS$

Table IIIe *Bilaterality (rheumatoid episcleritis and rheumatoid scleritis) 46 cases*

Disease	Cases	Percentage	Eye inflammation			
			Unilateral		Bilateral	
			No.	Per cent	No.	Per cent
Episcleritis	9	19.6	5	55.6	4	44.4
Scleritis	37	80.4	12	32.4	25	67.6

Table IIIf *Bilaterality (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases*

Disease	Cases	Percentage	Eye inflammation			
			Unilateral		Bilateral	
			No.	Per cent	No.	Per cent
Episcleritis	33	64.7	13	39.4	20	60.6
Scleritis	18	35.3	11	61.1	7	38.9

showed a similar number of unilateral and bilateral cases (5.4) but rheumatoid scleritis (37 cases) was more commonly bilateral (67.6 per cent). Non-rheumatoid episcleritis (33) was more commonly bilateral (39.4 to 60.6 per cent) and non-rheumatoid scleritis (18) was more often unilateral (61.1 to 38.9 per cent).

PAST MEDICAL HISTORY AND ASSOCIATED DISEASE (Tables IVa, b)

A breakdown of medical history and associated disease revealed a high incidence of associated abnormality of the cardiovascular and respiratory systems.

Of 30 cases with rheumatoid scleritis (60.0 per cent) in whom electrocardiograms were taken, 18 had ischaemic heart disease. Three further patients complained of angina pectoris but had normal tracings. Six patients with non-rheumatoid episcleritis (21.9 per cent) had electrocardiographic changes and one further patient had a possible pericarditis. Three patients with non-rheumatoid scleritis (16.7 per cent) had ischaemia of the myocardium. There is a significant difference between the incidence of ischaemia in rheumatoid scleritis and that in non-rheumatoid scleritis ($P=0.0005$). The combined episcleritis/scleritis groups showed a total incidence of myocardial ischaemia in 21 of 37 known cases (56.7 per cent) in comparison with the rheumatoid control group, eight of 20 known cases (40.0 per cent). It is interesting to note that only seven in the episcleritis/scleritis groups did not have an electrocardiogram compared with 16 in the matched control group. Does this reflect the fact that the groups with eye

inflammation were more often admitted to the wards, or does it indicate that there was more clinical indication for electrocardiography in the episcleritis/scleritis groups? Certainly clinical examination of the control group had given little evidence of severe cardiovascular disease. The

Table IVa *Past medical history and associated disease (rheumatoid episcleritis and scleritis) 46 cases*

Episcleritis (9 cases)			Scleritis 37 (cases)		
	No.	Per cent		No.	Per cent
Ischaemic heart disease, 7 cases (2 unknown)	3	42.9	Ischaemic heart disease, 30 cases (7 unknown)	18	60.0
Rheumatic fever	2	22.2	Hypertension, 32 cases (5 unknown)	8	25.0
Hypertension, 7 cases (2 unknown)	1	14.3	Angina pectoris (electrocardiogram normal)	3	8.1
Aortic stenosis	1		Cerebrovascular accident	3	
Cerebrovascular accident	1		Pericarditis	1	2.7
Raynaud's phenomenon	1		Mitral stenosis	1	
Pneumonia	1		Aortic stenosis and incompetence	1	
Pleural effusion	1		Rheumatic fever	1	
Pleurisy	1		Pulmonary embolus	1	
Sinusitis	1		Deep venous thrombosis	1	
Osteoarthritis	1		Pneumonia	5	13.5
Chronic renal disease	1		Pleural effusion	5	
Oral pemphigoid	1		Sinusitis	4	10.8
Gastric ulcer	1		Rheumatoid nodules of lung	3	
Recurrent colitis	1		Tuberculosis of lung	2	
Hemicolectomy	1		Emphysema	2	
Pelvic abscess	1		Asthma	1	
Diabetes	1		Pneumoconiosis	1	
Bilateral otitis media	1		Granulomatous (collagen) disease	1	
			Osteoarthritis	4	
			Dupuytren's contracture	1	
			Psoriatic arthritis	1	
			Duodenal ulcer	4	
			Cholecystectomy	3	
			Hysterectomy	3	
			Diverticulosis	1	
			Adenocarcinoma of bowel	1	
			Appendicectomy	1	
			Prostatectomy	1	
			Prolapsed bowel	1	
			Inguinal hernia	1	
			Hepatitis	1	
			Herpes zoster (trunk)	3	
			Psoriasis	1	
			Rodent ulcer	1	
			Thyrotoxicosis	1	
			Diabetes	1	
			Trigeminal neuralgia	1	
			Pernicious anaemia	1	
			Puerperal fever	1	
			Chronic otitis media	1	

statistically insignificant difference between these two groups might well be misleading.

Excluding respiratory complaints such as bronchitis, emphysema and asthma, pleurisy and rheumatoid pneumonia, pleural effusion, pleurisy and rheumatoid nodules of the lung, both rheumatoid episcleritis and scleritis had a similar incidence

Table IVb Past medical history and associated disease (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Episcleritis (33 cases)			Scleritis (18 cases)		
	No.	Per cent		No.	Per cent
Hypertension, 30 cases (3 unknown)	8	26.7	Hypertension, 16 cases (2 unknown)	4	25.0
Ischaemic heart disease, 32 cases (1 unknown)	6	18.8	Ischaemic heart disease	3	16.7
Valvular heart disease	2	6.1	Rheumatic fever	1	5.5
Rheumatic fever	2		Aortic incompetence	1	
Pericarditis	1	3.0	Migraine	1	
Cerebrovascular accident	1		Sinusitis	5	27.8
Sinusitis	8		Asthma	2	11.1
Pneumonia	2		Tuberculosis of chest	1	
Asthma	2		Bronchitis	1	
Bronchitis	1		Pneumonia	1	
Osteoarthritis	5	15.2	Osteoarthritis	3	16.7
'Rheumatism'	5		'Fibrositis'	2	
'Back trouble'	2		'Slipped disc'	1	
'Fibrositis'	2		'Rheumatism'	1	
'Knee synovitis'	1		Gout	1	
Cervical spondylosis	1		Menopausal haematuria	1	
Paget's disease of spine and ischium	1		Cholecystectomy	2	
Coccygodynia	1		Appendicectomy	2	
Patellar displacement	1		Hysterectomy	2	
Gout	1		Gastritis	1	
Pyelitis	2		'Gastric haemorrhage'	1	
Tuberculosis of kidneys	1		Duodenal ulcer	1	
Hydronephrosis	1		Apical dental abscess	1	
Renal stone	1		Systemic lupus erythematosus	1	
Duodenal ulcer	4	12.1	Erythema nodosa	1	
Hiatus hernia	2		Multiple rodent ulcers	1	
Cholecystitis	1		Jaundice	1	
Appendicectomy	1		Depression	1	
Perianal sinus	1				
Apical dental abscess	1				
Jaundice	1				
Thyroidectomy	1				
Erythema nodosa	2				
Chronic discoid lupus erythematosus	1				
Psoriasis	1				
Pityriasis rosea	1				
Ulcer inguinal region	1				
Acne rosacea	1				
Herpes zoster ophthalmicus	1				
Diabetes	1				
Glandular fever	1				
Puerperal fever	1				

of respiratory complications – that is, three of nine cases in episcleritis (33.3 per cent) and 13 of 37 cases in scleritis (35.1 per cent). The incidence of respiratory disease in non-rheumatoid episcleritis and scleritis was much lower; two of 33 cases in episcleritis (6.1 per cent) and one of 18 cases in scleritis (5.6 per cent). The difference in each case is statistically significant ($P=0.05$ and $P=0.025$, respectively). The combined rheumatoid episcleritis/scleritis groups gave a total of 16 with rheumatoid respiratory complaints out of 46 cases (34.8 per cent) as compared with five of 45 rheumatoid controls (11.1 per cent). The difference is statistically significant ($P=0.01$).

Other associated systemic disorders are listed in Tables IVa, b.

EYE SYMPTOMS (Tables Va, b)

Redness and ocular pain are by far the commonest complaints in both episcleritis and scleritis. A red eye was referred to only slightly less often in rheu-

Table Va Eye symptoms (rheumatoid episcleritis and rheumatoid scleritis) 44 cases

Symptoms	Episcleritis (9 cases)		Scleritis (35 cases, 2 unknown)	
	No.	Per cent	No.	Per cent
Red, inflamed, bloodshot	8	88.9	29	82.9
Ocular pain	3	33.3	16	45.7
Gritty, sandy	2	22.2	11	31.4
Burning	1	11.1	5	14.3
Itching	0		3	8.6
Watering	1		3	
Irritation	1		2	5.7
Photophobia	0		2	
Oedema of lids	0		2	
Headache	0		2	
Discharge, mattering	1		1	2.9
Dryness	1		1	
Blurring of vision	0		1	

Table Vb Eye symptoms (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Symptoms	Episcleritis (33 cases)		Scleritis (18 cases)	
	No.	Per cent	No.	Per cent
Red, inflamed, bloodshot	31	93.9	16	88.9
Ocular pain	16	48.5	13	72.2
Gritty, sandy	8	24.2	3	16.7
Headache	4	12.1	1	5.6
Oedema of lids	4		0	
Irritation	3	9.1	3	
Discharge, mattering	3		0	
Burning	2	6.1	2	11.1
Watering	2		0	
Dryness	1	3.0	1	
Blurring of vision	1		1	
Itching	0		1	
Photophobia	0		0	

matoid episcleritis (88.9 per cent) than in non-rheumatoid episcleritis (93.9 per cent), and in rheumatoid scleritis (82.9 per cent) compared with non-rheumatoid scleritis (88.9 per cent). A greater disparity of complaint was notable with regard to ocular pain in rheumatoid episcleritis (33.3 per cent) compared with non-rheumatoid episcleritis (48.5 per cent), and in rheumatoid scleritis (45.7 per cent) compared with non-rheumatoid scleritis (72.2 per cent). The lower incidence of complaint by rheumatoid patients probably reflects the measure of discomfort they experience elsewhere.

LENGTH OF HISTORY OF EYE INFLAMMATION (Tables VIa, b)

Figures giving the duration of ocular inflammation must be interpreted cautiously, as it is impossible to know whether the inflammation is truly quiescent. However, in each of the four groups of patients the mean duration (with a large standard deviation in each case) showed no significant difference. It was interesting to note that the mean duration of ocular inflammation in the rheumatoid patients was shorter than that in the non-rheumatoid patients; 36.2 months (rheumatoid episcleritis) and 35.0 months (rheumatoid scleritis) compared with 42.4 months (non-rheumatoid episcleritis) and 48.9 months (non-rheumatoid scleritis). There was a wide range in each group, from a few days or weeks to 23½ years.

Table VIa *Length of history of eye inflammation (rheumatoid episcleritis and rheumatoid scleritis) 40 cases*

Disease	Cases	Range	Mean (months)	SD	SEM
Episcleritis	8 (1 unknown)	3 days/ 15 years	36.2	±60.0	±21.2
Scleritis	32 (5 unknown)	1 week/ 20 years	35.0	±54.0	±9.6

Statistical analysis: $t=0.0534$; $P=NS$

Table VIb *Length of history of eye inflammation (non-rheumatoid episcleritis and non-rheumatoid scleritis) 49 cases*

Disease	Cases	Range	Mean (months)	SD	SEM
Episcleritis	31 (2 unknown)	4 weeks/ 23½ years	42.4	±74.2	±13.3
Scleritis	18	7 weeks/ 20 years	48.9	±74.2	±17.5

Statistical analysis: $t=0.2938$; $P=NS$

Statistical analysis (rheumatoid versus non-rheumatoid):

Episcleritis: $t=0.1139$; $P=NS$

Scleritis: $t=0.5713$; $P=NS$

VISUAL ACUITY (Table VII)

Visual acuity was recorded in the Tennent Institute of Ophthalmology but it was not recorded routinely in patients seen at the Centre for Rheumatic Diseases. An arbitrary dividing line of visual acuity of 6/12 (Snellen), or worse, provided a parameter for

Table VII *Visual acuity (Tennent Institute of Ophthalmology) 62 cases*

Disease	Eyes (total no.)	No. of eyes with visual acuity < 6/9	Percentage
Episcleritis	56	8	14.3
Scleritis	41	15	36.6

Statistical analysis (episcleritis versus scleritis):

$\chi^2=6.5070$; $P=0.025$

the level of visual acuity achieved by each patient. Of the total of 56 eyes with episcleritis, eight eyes (14.3 per cent) had a visual acuity of 6/12 or worse, and of the 41 eyes with scleritis, 15 (36.6 per cent) had a visual acuity of 6/12 or worse. The difference between these two groups is statistically significant ($P=0.025$). It must be emphasized that refraction was not done as a routine in these cases and that the difference is based on the patient's best visual acuity either with distance glasses or without.

TYPE OF INFLAMMATION (Tables VIIIa, b)

All nine cases of rheumatoid episcleritis were of the 'simple' variety. Nodular episcleritis was noted in six cases (18.2 per cent) of the patients with non-rheumatoid inflammation (Fig. 1) and simple episcleritis was recorded in 27 (81.8 per cent). Diffuse scleritis (Fig. 2) was more common in rheumatoid scleritis (83.3 per cent) and non-rheumatoid scleritis (61.1 per cent). A nodular scleritis was slightly less common in rheumatoid scleritis (16.7 per cent) as compared with non-rheumatoid scleritis (33.3 per cent). One case of non-rheumatoid necrotizing scleritis (Fig. 3) presented in a patient who had developed gout some months earlier, but the area of necrotic sclera was

Table VIIIa *Type of inflammation (rheumatoid episcleritis and rheumatoid scleritis) 45 cases*

Disease	Cases	Per cent	Type	Per cent
Episcleritis	9		Nodular	0
			Simple	9
Scleritis	36 (1 unknown)		*Nodular	6 16.7
	Anterior	36 100	Diffuse	30 83.3
	Posterior	8 22.2	Necrotizing	0

*Scleral translucency in 29 cases (80.6 per cent)

Table VIIIb *Type of inflammation (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases*

Disease	Cases		Per cent	Type	Per cent
Episcleritis	33			Nodular	6 18.2
				Simple	27 81.8
Scleritis	18			Nodular	6 33.3
	Anterior	18	100*	Diffuse	11 61.1
	Posterior	1	5.6	Necrotizing	1 5.6

*Scleral translucency in two cases (11.1 per cent)

probably determined by a subconjunctival injection of methylprednisolone some days previously. Co-existent posterior scleritis was more common in rheumatoid scleritis (22.2 per cent) than in non-rheumatoid scleritis (5.6 per cent). The figure of eight cases in rheumatoid inflammation was a tentative one, based on two cases of choroiditis, one case of retinal detachment, and five cases of extraocular muscle imbalance, suggesting tendon

FIG. 1 *Nodular non-rheumatoid episcleritis*

FIG. 3 *Necrotizing scleritis*

or muscle involvement. These figures do not include patients with macular disturbance which might have been due to other causes. The section on posterior segment abnormality will deal with this in more detail. One of the most interesting findings was the difference between rheumatoid and non-rheumatoid scleritis in the incidence of scleral translucency (Fig. 2). Of 36 cases with rheumatoid scleritis, 29 (80.6 per cent) showed scleral translucency as compared with two of 18 cases with non-rheumatoid scleritis (11.1 per cent).

DISTRIBUTION OF INFLAMMATION (Tables IXa, b)

The distribution of ocular inflammation in episcleritis is more commonly in the interpalpebral area, suggesting the possibility of external aggravating factors. Scleritis will also affect the superior quadrants of the eye in particular, although less markedly so in non-rheumatoid scleritis. Rheuma-

FIG. 2 *Bilateral diffuse scleritis*

Tables IXa, b *Distribution of inflammation*

toid scleritis has a fairly even distribution affecting all quadrants of the anterior sclera.

CORNEAL COMPLICATIONS (Tables Xa, b)

An unexpected finding among the rheumatoid patients was a higher percentage of corneal complications in episcleritis (69.2 per cent) compared with scleritis (43.5 per cent). The small number of 13 eyes with episcleritis, however, may have given an inaccurate picture when one considers the anatomy of the structures involved. The difference is not statistically significant. Non-rheumatoid inflammation showed a lower percentage of corneal involvement in episcleritis (18.9 per cent) than in scleritis (28.0 per cent) although the difference was

not statistically significant. Corneal complications showed a higher incidence in rheumatoid as compared with non-rheumatoid disease, which was statistically significant for episcleritis ($P=0.0005$) but not for scleritis.

The predominant corneal complication is a sclerosing keratitis which is usually localized at the site nearest to the inflamed sclera or episclera. Occasionally, in diffuse inflammation, the condition is annular (Fig. 4). The scar of sclerosing keratitis is permanent but in itself has little effect on visual acuity. However, of 10 patients with annular sclerosing keratitis in whom visual acuity was assessed, six (60.0 per cent) had markedly reduced vision due to lens changes.

Limbal guttering occurred in one eye with rheu-

FIG. 4 *Annular sclerosing keratitis in a patient with non-rheumatoid scleritis*

Table Xa Corneal complications (rheumatoid episcleritis and rheumatoid scleritis) 46 cases

Disease	Eyes (no.)	Eye inflammation		Bilateral	Cases (no.)	Per-centage
		Unilateral	Cases (no.)			
Episcleritis	13	Localized stromal	1*	Localized sclerosing	3	69.2
		Localized sclerosing	1			
		Annular sclerosing	1			
Scleritis	62	Localized sclerosing	2	Localized sclerosing	6	43.5
		Annular sclerosing	1	Annular sclerosing	4	
		Keratolysis	1	Grossly degenerate blind	1	
				Localized sclerosing	1*	

Three eyes with scleritis (4.9 per cent) and one with episcleritis (7.6 per cent) developed a limbal gutter at the site of sclerosing keratitis

Statistical analysis: $\chi^2=2.8399$; $P=NS$

In all unilateral cases and one bilateral case (marked with asterisk) only one eye was affected

Table Xb Corneal complications (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Disease	Eyes (no.)	Eye inflammation		Bilateral	Cases (no.)	Per-centage
		Unilateral	Cases (no.)			
Episcleritis	53			Localized sclerosing	2*	18.9
				Localized sclerosing	2	
				Annular sclerosing	1*	
				Limbal guttering	1	
				Band keratopathy	1	
Scleritis	25	Localized sclerosing	3	Annular sclerosing	2*	28.0

Statistical analysis: $\chi^2=0.8311$; $P=NS$

Statistical analysis (rheumatoid versus non-rheumatoid):

Episcleritis: $\chi^2=12.9161$; $P<0.0005$

Scleritis: $\chi^2=1.8091$; $P=NS$

*Both eyes were affected

FIG. 5 Limbal guttering in a patient with rheumatoid episcleritis

matoid episcleritis, three eyes with rheumatoid scleritis (Fig. 5), and one eye with non-rheumatoid episcleritis. Apart from the last case, each occurred at the site of an area of sclerosing keratitis. A localized stromal keratitis occurred deep in the mid-stroma in one patient with rheumatoid episcleritis. One patient with rheumatoid scleritis had a perforating keratolysis, which is the corneal counterpart of a perforating scleritis.

ANTERIOR UVEITIS (Tables XIa, b)

The percentage of eyes with active uveitis or evidence of old uveitis was slightly lower in rheumatoid episcleritis (23.1 per cent) compared with rheumatoid scleritis (28.3 per cent). The difference is not statistically significant. A similar picture emerged in non-rheumatoid episcleritis (17.0 per cent) and non-rheumatoid scleritis (20.0 per cent). Posterior synechiae suggesting a more active and plastic type of uveitis were found in seven of 17 eyes with rheumatoid scleritis (41.2 per cent) as compared with one eye with posterior synechiae associated with non-rheumatoid scleritis (20.0 per cent).

CATARACT (Table XII)

The findings as regards the development of cataract in patients with rheumatoid scleritis who had

Table XIa Anterior uveitis (rheumatoid episcleritis and rheumatoid scleritis) 45 cases

Disease	Eyes (no.)	Eye inflammation		Bilateral	Cases (no.)	Per-centage
		Unilateral	Cases (no.)			
		Affected eyes		Affected eyes		
Episcleritis	13	—	—	2*	1	23.1
				1	1	
Scleritis	60	1	1	2	6	28.3
	(2 unknown)			1	4	

Statistical analysis: $\chi^2=0.1484$; $P=NS$

Table XIb Anterior uveitis (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Disease	Eyes (no.)	Eye inflammation		Bilateral	Cases (no.)	Per-centage
		Unilateral	Cases (no.)			
		Affected eyes		Affected eyes		
Episcleritis	53	1	3	2	2	17.0
				1	2	
Scleritis	25	1	4	1	1	20.0

Statistical analysis: $\chi^2=0.1051$; $P=NS$

Statistical analysis (rheumatoid versus non-rheumatoid):

Episcleritis: $\chi^2=0.2608$; $P=NS$

Scleritis: $\chi^2=0.6388$; $P=NS$

Table XII *Posterior subcapsular cataract (PSC) in patients receiving systemic corticosteroids*

<i>Rheumatoid scleritis</i>	<i>Cases (no.)</i>	<i>Mean age $\pm$ SD</i>	<i>Sex ratio F/M</i>	<i>PSC</i>	<i>Per-centage</i>
Patients	25	55.89 $\pm$ 12.99	3.5/1	9	36.0
'Control' group	148	52.5 $\pm$ 11.5	9.6/1	17	11.5

Statistical analysis: $\chi^2 = 10.0639$; $P = < 0.005$

received treatment with systemic corticosteroids are of particular interest. The incidence of posterior subcapsular cataract in patients with rheumatoid scleritis who had been treated with systemic corticosteroids was high (36.0 per cent). Nine of 25 patients who had received treatment with systemic corticosteroids had developed posterior subcapsular cataract. There were three further patients who had advanced cataract, two of whom had bilateral cataract (one had one aphakic eye), but these are not included for the purposes of statistical analysis. A previous study involving two of us (JW and DDMM), of the incidence of steroid-induced cataract in patients with rheumatoid arthritis, found that 17 of 148 patients with rheumatoid arthritis (11.5 per cent) who had received systemic corticosteroids had posterior subcapsular cataracts. These patients also attended the Centre for Rheumatic Diseases, Glasgow. Comparison of the incidence of posterior subcapsular cataract in rheumatoid scleritis (36.0 per cent) with posterior subcapsular cataract in patients with rheumatoid arthritis without scleritis (11.5 per cent), both groups receiving systemic corticosteroid treatment, is statistically significant ($P = 0.005$).

Only three other patients in the study had the characteristic form of cataract. One patient with rheumatoid episcleritis had bilateral posterior subcapsular cataract and had been treated with systemic corticosteroids for an uncertain length of time. It is interesting that of 51 patients with non-rheumatoid episcleritis or scleritis, two patients developed posterior subcapsular cataract, and these were the only two patients of the non-rheumatoid group who were receiving systemic corticosteroid treatment.

POSTERIOR SEGMENT ABNORMALITY (Tables XIIIa, b)

No patient with rheumatoid episcleritis had abnormality of the posterior segment of the eye. However, the percentage of abnormal features in association with rheumatoid scleritis was 29.1 per cent. The commonest abnormality was a macular disturbance in 11 eyes (20.0 per cent), although three of these eyes were myopic, and this might have affected their macular state. The origin of macular disturbance is difficult to determine in these cases, and the

results need to be viewed with caution. Many of the rheumatoid patients received a number of different antirheumatic drugs which might have disturbed the retinal picture. However, macular disturbance is a recognized complication of scleritis (Watson and Lobascher, 1965). Two eyes showed old foci of choroiditis and one eye, in a patient now deceased, optic atrophy of obscure origin, although the eye had been grossly inflamed and suffered a subsequent perforating keratolysis. It was interesting to find oedema of the optic nerve head in one case, suggesting a possible ischaemic optic neuropathy. One patient had an old detached retina.

There was an area of old choroiditis in one case diagnosed as non-rheumatoid episcleritis (1.9 per cent of 52 eyes). Two eyes with non-rheumatoid scleritis had a possibly significant abnormality of the posterior pole (8.0 per cent of 25 eyes); in both cases these were areas of macular disturbance.

There was a marked difference in the incidence of abnormality between rheumatoid episcleritis and scleritis. The significant difference between posterior segment complications in rheumatoid scleritis and non-rheumatoid scleritis ($P = 0.05$) may reflect more severe disease in the rheumatoid patient.

INTRAOCULAR PRESSURE (Tables XIVa, b)

One patient with rheumatoid episcleritis had bilateral raised intraocular pressure, but this was

Table XIIIa *Posterior segment abnormality (rheumatoid episcleritis and rheumatoid scleritis) 42 cases*

<i>Episcleritis 9 eyes (4 unknown)</i>	<i>Scleritis 55 eyes (7 unknown)*</i>	<i>Per-centage</i>
—	Macular disturbance	11 20.0†
	Old choroiditis	2 4.2
	Optic atrophy	1 2.1
	Oedema of optic nerve head	1
	Old detached retina	1
		29.1

*Two cases were obscured by cataract

†Three eyes were myopic

Table XIIIb *Posterior segment abnormality (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases*

<i>Episcleritis 52 eyes (1 unknown)</i>	<i>Per-centage*</i>	<i>Scleritis 25 eyes</i>	<i>Per-centage</i>
Old choroiditis	1 1.9	Macular disturbance	2 8.0

*One case obscured by band keratopathy

Statistical analysis: $\chi^2 = 1.6651$; $P = \text{NS}$

Statistical analysis (rheumatoid versus non-rheumatoid):

Scleritis: $\chi^2 = 4.3844$; $P = < 0.05$

Table XIVa Raised intraocular pressure* (rheumatoid episcleritis and rheumatoid scleritis) 37 cases

		Eye inflammation						
Disease	Eyes (no.)	Unilateral			Bilateral			Percentage
		Cases	Eyes affected	IOP mmHg	Cases	Eyes affected	IOP mmHg	
Episcleritis	9 (4 unknown)	1	2	26 +25	—			—
Scleritis	48 (14 unknown)	1	1	22	2	2	29 +32 26 +23 22 Absolute glaucoma 22 32	18.7

*The highest reading recorded is given in each case

†A case of closed-angle glaucoma not considered as positive as the raised pressure was not due to inflammation

Table XIVb Raised intraocular pressure (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Disease	Eyes (no.)	Eye inflammation						Percentage
		Unilateral			Bilateral			
		Cases	Eyes affected	IOP mmHg	Cases	Eyes affected	IOP mmHg	
Episcleritis	53	—			1	1	22	1.9
Scleritis	25	3	1	26 30 38 30 +28 30 +34	—			12.0
		2	2*					

*Both these cases, although unilateral cases of scleritis, received topical steroids to both eyes. On withdrawing topical steroids all four eyes reverted to normal intraocular pressures. They are considered cases of steroid-induced glaucoma and not primarily due to inflammation. Statistical analysis (rheumatoid versus non-rheumatoid): Scleritis, $\chi^2=0.5453$; $P=NS$

due to closed-angle glaucoma and the condition settled with bilateral peripheral iridectomies. No other patient with rheumatoid episcleritis had raised intraocular pressure. Nine eyes with rheumatoid scleritis (18.7 per cent) had raised intraocular pressure; in two cases there was absolute glaucoma. Four eyes had levels recorded by applanation tonometry at or between 22 and 26 mmHg. One eye, with a reading at 22 mmHg, was a case of old 'burnt out' absolute glaucoma. One eye had a reading at 29 mmHg, one at 30 mmHg, and two at 32 mmHg.

Only one patient with non-rheumatoid episcleritis had one eye with a tension fractionally above normal at 22 mmHg, a percentage of 1.9 per cent. Seven eyes with non-rheumatoid scleritis had raised levels but in two cases (four eyes) the level of pressure fell from 30 mmHg (right) + 28 mmHg (left) and 30 mmHg (right) + 34 mmHg (left) to within normal limits on withdrawing topical steroid treatment. It is considered that these were cases of steroid-induced glaucoma. The remaining three cases (12.0 per cent) include one patient in whom the intraocular pressure was 38 mmHg. In each case the highest reading recorded is given.

Only one patient, a woman with unilateral rheumatoid scleritis, required a drainage procedure to control her intraocular pressure. There was no flare-up of her scleritis. One patient with a pressure at 22 mmHg in one eye is still receiving miotic treatment. The intraocular pressure of the remaining patients all settled coincident with the quietening of their inflammation, including those patients in whom pressures were recorded in the 30–38 mmHg range.

OCULAR MOVEMENTS (Tables XVa, b)

No patient with rheumatoid episcleritis had evidence of muscle imbalance. Eight eyes with rheumatoid scleritis (12.9 per cent) showed limitation of movement of one extraocular muscle or more. Two cases, however, were based on a history of transient diplopia, suggesting tendon or muscle involvement consistent with the site of scleral inflammation. The limitation of movement in the remaining six cases was substantiated by orthoptic examination.

Three cases of non-rheumatoid episcleritis (5.7 per cent) suggested possible tendon and/or muscle

Table XVa Ocular movements (rheumatoid episcleritis and rheumatoid scleritis) 46 cases

Disease	Eyes (no.)	Muscle imbalance	Percentage
Episcleritis	13	—	—
Scleritis	62	8*	12.9

*Two cases based on history of transient diplopia

Table XVb Ocular movement (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Disease	Eyes (no.)	Muscle imbalance	Percentage
Episcleritis	53	3*	5.7
Scleritis	25	6†	24.0

*All three cases tentatively based on history of transient diplopia

†One case based on a history of intermittent diplopia

Statistical analysis (non-rheumatoid episcleritis versus non-rheumatoid scleritis): $\chi^2 = 5.5976$; $P = < 0.025$

Statistical analysis (rheumatoid versus non-rheumatoid):

Scleritis: $\chi^2 = 1.6248$; $P = \text{NS}$

inflammation, but the conclusion is tentative. All three cases gave a brief history of diplopia which they associated with an inflamed eye. Six cases with non-rheumatoid scleritis (24.0 per cent) gave evidence of tendon and/or muscle imbalance, one case based on an account of intermittent diplopia and the remaining five cases confirmed by an orthoptic assessment. The difference in incidence between non-rheumatoid episcleritis and non-rheumatoid scleritis is statistically significant ($P = 0.025$).

One patient, a 34-year-old woman who had non-rheumatoid scleritis presented with a dramatic strabismus. Examination revealed a paresis of the left lateral rectus muscle. This was the third time in three years that she had had an inflamed eye. On the first occasion there had been a paresis of the right medial rectus muscle. A biopsy (1×3 mm) of the middle section of tendon and muscle of the left lateral rectus muscle confirmed the presence of a tenosynovitis. Chemosis was characteristic of each episode after a few days of ocular pain, and on each occasion was thought to herald the onset of an orbital cellulitis.

KERATOCONJUNCTIVITIS SICCA (Tables XVIa, b)

One patient with rheumatoid episcleritis (14.2 per cent) had definite KCS, and four patients with rheumatoid scleritis (12.9 per cent). Of the patients with non-rheumatoid inflammation, four with episcleritis (12.1 per cent), and one with scleritis (5.6 per cent) had KCS.

There were three further cases of possible KCS. One case was associated with rheumatoid episcleritis and two cases with rheumatoid scleritis. In each

the Schirmer I tear test was markedly reduced. All three patients had died before complete examination could be carried out and no Schirmer II test or rose bengal staining had been done.

SJÖGREN'S SYNDROME

Sjögren's syndrome is defined as a triad of features; KCS, xerostomia (with or without salivary gland swelling), and a connective-tissue disease. The presence of either KCS or xerostomia with a systemic disorder is accepted as sufficient (Bloch, Buchanan, Wohl, and Bunim, 1965).

Only two of the 37 cases of rheumatoid scleritis exhibited the triad of dry eyes, dry mouth, and a connective-tissue disorder (in this case rheumatoid arthritis). No case of rheumatoid episcleritis had the triad of features of Sjögren's syndrome. However, two further cases of rheumatoid scleritis and one case of rheumatoid episcleritis had KCS associated with the systemic disease. Eight further cases of rheumatoid scleritis and two cases of rheumatoid episcleritis also had xerostomia with rheumatoid arthritis. This means that the total incidence of Sjögren's syndrome, according to the criteria given, is 12 of 37 cases of rheumatoid scleritis (32.4 per cent) and three of nine cases of rheumatoid episcleritis (33.3 per cent).

SICCA SYNDROME

One patient with non-rheumatoid episcleritis (3.0 per cent) had dry eyes combined with a dry

Table XVIa Keratoconjunctivitis sicca (rheumatoid episcleritis and rheumatoid scleritis) 42 cases

Disease	Cases (no.)	No. of KCS cases	Percentage
Episcleritis	8 (1 unknown)*	1	14.2
Scleritis	34 (3 unknown)†	4	12.9

*The 'unknown' case had a markedly reduced Schirmer I test

†Two 'unknown' cases had markedly reduced Schirmer I tests (one case is included as a positive KCS because of a reduced Schirmer I test with widespread rose bengal staining)

Statistical analysis: $\chi^2 = 0.006$; $P = \text{NS}$

Table XVIb Keratoconjunctivitis sicca (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Disease	Cases (no.)	No. of KCS cases	Percentage
Episcleritis	33	4	12.1
Scleritis	18	1	5.6

Statistical analysis: $\chi^2 = 0.5678$; $P = \text{NS}$

Statistical analysis (rheumatoid versus non-rheumatoid):

Episcleritis: $\chi^2 = 0.0247$; $P = \text{NS}$

Scleritis: $\chi^2 = 0.6710$; $P = \text{NS}$

Table XVII Articular features of patients with rheumatoid episcleritis and rheumatoid scleritis

Features	Rheumatoid episcleritis/scleritis					Rheumatoid controls					P value
	No. of cases	Range (years)	Mean (years)	SD	SEM	No. of cases	Range (years)	Mean (years)	SD	SEM	
Duration of rheumatoid arthritis	46	0.5-50	14.5	±12.9	±1.9	46	0.17-48	9.2	±10.2	±1.5	<0.05
Functional class	45	1-4	2.7	±0.9	±0.14	46	1-4	2.28	±0.78	±0.11	NS
Articular index	43	0-78	23.1	±20.0	±3.1	41	0-53	19.0	±12.9	±2.0	NS
X-ray stage	36	1-4	2.97	±0.61	±0.1	38	1-4	2.42	±1.03	±0.17	<0.01

NS = Not significant

mouth, features of the sicca syndrome, in which the dryness of mucous membranes is not associated with a connective-tissue disorder.

RHEUMATOLOGY

The following data refer to those patients with rheumatoid episcleritis or rheumatoid scleritis and compare them with a group of rheumatoid controls, matched for age and sex—that is, patients with rheumatoid arthritis but with no evidence of episcleral or scleral inflammation. For the purposes of this paper, as regards the articular and extra-articular features of rheumatoid disease, the patients with rheumatoid episcleritis and scleritis are combined as one group and compared with the rheumatoid control group.

DURATION OF RHEUMATOID ARTHRITIS; FUNCTIONAL CLASS; ARTICULAR INDEX, AND X-RAY STAGE (Table XVII)

The range of duration was huge in both rheumatoid episcleritis/scleritis and in rheumatoid controls, from a few months to 50 years. However, episcleritis and scleritis occurred in patients with longer-standing rheumatoid arthritis (mean values 14.5 years compared with 9.2 years). The difference is statistically significant ($P=0.05$).

The functional class measures in four grades of increasing severity the degree of functional incapacity due to arthritis. The study of functional

incapacity was the only investigation in which the rheumatoid control group showed a more severe degree of abnormality compared with the rheumatoid episcleritis/scleritis group. The mean value for 45 known cases of rheumatoid episcleritis/scleritis was 2.17 and for 46 cases in the rheumatoid control group was 2.28.

The articular index records the number of involved joints and the severity of their involvement as judged by tenderness to pressure over the joint margin. The matched group of rheumatoid controls had a mean value of 19. The difference between the control group and the combined rheumatoid episcleritis/scleritis group (mean value: 23.1) was not statistically significant.

The x-ray stage indicates radiologically the degree of bone and joint involvement categorized in four stages of increasing severity. Comparison of the rheumatoid episcleritis/scleritis group (mean value: 2.97) and the group of rheumatoid controls (mean value: 2.42) indicated that episcleritis and scleritis occurred in a group with more severe erosive arthritis. The difference is statistically significant ($P=0.01$).

SUBCUTANEOUS NODULES; PERIPHERAL NEUROPATHY; SKIN ULCERS; SKIN BRUISING; SKIN ATROPHY; AMYLOID; TENDON RUPTURE AND SPLENOMEGALY (Table XVIII)

Of 46 cases with rheumatoid episcleritis or scleritis 23 had subcutaneous granulomatous nodules

Table XVIII Extra-articular features in patients with rheumatoid episcleritis and rheumatoid scleritis

Extra-articular features	Rheumatoid episcleritis/scleritis			Rheumatoid controls			P value
	No. of cases	No. of cases positive	Per cent	No. of cases	No. of cases positive	Per cent	
Subcutaneous nodules	46	23	50.0	46	11	23.9	<0.01
Peripheral neuropathy	45	3	8.9	46	1	2.2	NS
Skin ulcers	45	6	13.3	46	2	4.4	NS
bruising	46	11	23.9	46	5	10.9	NS
atrophy	46	16	34.8	46	5	10.9	<0.01
Amyloid	46	2	4.4	46	0	—	—
Splenomegaly	46	5	10.9	46	1	2.2	NS
Tendon rupture	46	0	—	46	0	—	—

(50.0 per cent). Comparison with the incidence in the rheumatoid control group (23.9 per cent) showed a statistically significant difference ($P=0.01$).

Three of 45 known cases of rheumatoid episcleritis or scleritis (8.9 per cent) revealed a high incidence of peripheral neuropathy as compared with only one case in the rheumatoid control group (2.2 per cent). However, the difference is not statistically significant. Two of the patients with rheumatoid episcleritis/scleritis had received treatment with systemic corticosteroids and two had been given gold therapy (one patient had received both). Either of these treatments could have produced neuropathy. The patient in the rheumatoid control group had not received systemic treatment with corticosteroids or gold.

Six of 45 known cases with rheumatoid episcleritis or scleritis (13.3 per cent) had skin ulceration as compared with two of 46 cases in the rheumatoid control group (4.4 per cent). The difference is not statistically significant for these numbers. Three of the patients with rheumatoid episcleritis or scleritis had received treatment with systemic corticosteroids and both patients in the rheumatoid control group had received similar medication.

Skin bruising occurred more often in patients with rheumatoid episcleritis or scleritis (11 cases; 23.9 per cent) as compared with the rheumatoid controls (5 cases; 10.9 per cent). The difference for these numbers is not statistically significant. Ten of the patients in the rheumatoid episcleritis/scleritis group had received treatment with systemic corticosteroids and four of the five positive cases in the rheumatoid control group had been similarly treated.

Skin atrophy was found in 16 patients in the rheumatoid episcleritis/scleritis group (34.8 per cent) as compared with five patients in the rheumatoid control group (10.9 per cent); this is statistically significant ($P=0.01$). Ten of the patients in the

rheumatoid episcleritis/scleritis group and five in the rheumatoid control group had been given systemic corticosteroid treatment.

There were two men considered as having secondary amyloidosis; both had bilateral rheumatoid scleritis. One case was confirmed by liver biopsy. No case of amyloidosis was confirmed in the group of rheumatoid controls.

No patient with rheumatoid episcleritis/scleritis and none of the rheumatoid control group suffered tendon rupture.

The incidence of splenomegaly in the rheumatoid episcleritis/scleritis group was five of 46 cases (10.9 per cent). Only one patient of 46 rheumatoid controls (2.2 per cent) had a palpable spleen. The difference for these numbers is not statistically significant.

Laboratory investigations

The following data record information found in six groups of patients; patients with rheumatoid episcleritis and rheumatoid scleritis, non-rheumatoid episcleritis and non-rheumatoid scleritis, and patients with rheumatoid episcleritis and scleritis combined as one group for comparison with the rheumatoid control group.

HAEMOGLOBIN; ERYTHROCYTE SEDIMENTATION RATE (ESR); ALBUMIN/GLOBULIN RATIO; ALKALINE PHOSPHATASE; URIC ACID; SERUM GLUTAMIC OXALACETIC TRANSAMINASE (SGOT), and SERUM GLUTAMIC PYRUVIC TRANSAMINASE (SGPT) (Tables XIXa, b, c)

For the purposes of comparison haemoglobin results for both men and women are grouped together. In patients with rheumatoid episcleritis the mean value was 87.6 per cent but in those with rheumatoid scleritis it was 83.4 per cent. The mean haemoglobin value for patients with non-

Table XIXa *Laboratory investigations in patients with rheumatoid episcleritis and rheumatoid scleritis*

Laboratory investigation	Rheumatoid episcleritis				Rheumatoid scleritis				P value
	No. of cases	Mean	SD	SEM	No. of cases	Mean	SD	SEM	
Haemoglobin ESR	9	87.6 per cent	± 15.4	± 5.1	37	83.4 per cent	± 18.2	± 3.0	NS
	7	74.4 mm/1st h (Westergren)	± 37.9	± 14.3	30	65.3 mm/1st h (Westergren)	± 36.1	± 6.6	NS
Albumin/globulin ratio	9	0.88	± 0.37	± 0.12	37	1.03	± 0.41	± 0.07	NS
Alkaline phosphatase	9	12.07 KA units	± 4.73	± 1.58	37	14.68 KA units	± 12.73	± 2.09	NS
Uric acid	8	4.6 mg/100 ml	± 1.66	± 0.59	35	4.88 mg/100 ml	± 1.47	± 0.25	NS
SGOT	8	17.88 IU/l	± 8.17	± 2.89	30	29.33 IU/l	± 43.23	± 7.89	NS
SGPT	8	15.88 IU/l	± 12.86	± 4.55	30	23.87 IU/l	± 36.3	± 6.63	NS

Normal values: haemoglobin 90-125 per cent male, 80-110 per cent female; ESR 5-12 mm/1st h male, 0-7 mm female; A/G ratio 1.03-2.36 g/100 ml; alkaline phosphatase 5-15 KA units; uric acid 2.2-7.2 mg/100 ml male, 0.5-5.7 mg/100 ml female; SGOT 11-35 IU/l; SGPT 4-28 IU/l

Table XIXb Laboratory investigations in patients with non-rheumatoid episcleritis and non-rheumatoid scleritis

Laboratory investigations	Non-rheumatoid episcleritis				Non-rheumatoid scleritis				P value
	No. of cases	Mean	SD	SEM	No. of cases	Mean	SD	SEM	
Haemoglobin	31	99.9 per cent	±9.2	±1.6	18	98.4 per cent	±8.0	±1.9	NS
ESR	27	13.3 mm/1st h (Wintrobe)	±12.8	±2.5	15	19.9 mm/1st h (Wintrobe)	±13.0	±3.4	NS
Albumin/globulin ratio	33	1.75	±0.38	±0.07	18	1.53	±0.33	±0.08	<0.05
Alkaline phosphatase	33	7.36 KA units	±2.61	±0.45	18	8.06 KA units	±3.33	±0.79	NS
Uric acid	33	5.39 mg/100 ml	±1.90	±0.33	18	4.41 mg/100 ml	±1.25	±0.29	NS
SGOT	32	20.56 IU/l	±7.9	±1.4	18	22.67 IU/l	±16.04	±3.78	NS
SGPT	32	19.88 IU/l	±9.13	±1.61	18	19.39 IU/l	±12.7	±2.99	NS

Normal values are given with Table XIXa

Table XIXc Laboratory investigations in patients with rheumatoid episcleritis and rheumatoid scleritis: comparison with rheumatoid controls

Laboratory investigations	Rheumatoid episcleritis/scleritis				Rheumatoid controls				P value
	No. of cases	Mean	SD	SEM	No. of cases	Mean	SD	SEM	
Haemoglobin	46	84.3 per cent	±17.6	±2.6	45	90.1 per cent	±12.3	±1.83	NS
ESR	37	67.1 mm/1st h (Westergren)	±36.1	±5.9	45	48.4 mm/1st h (Westergren)	±34.1	±5.1	<0.025
Albumin/globulin ratio	46	1.0	±0.4	±0.06	40	1.12	±0.39	±0.06	NS
Alkaline phosphatase	46	14.2 KA units	±11.6	±1.7	41	11.5 KA units	±3.7	±0.58	NS
Uric acid	43	4.8 mg/100 ml	±1.5	±0.23	40	4.36 mg/100 ml	±1.14	±0.18	NS
SGOT	38	26.9 IU/l	±38.7	±6.3	27	14.6 IU/l	±5.1	±1.0	NS
SGPT	38	22.2 IU/l	±32.8	±5.3	23	12.0 IU/l	±5.5	±1.1	NS

Normal values are given with Table XIXa

rheumatoid episcleritis was 99.9 per cent, significantly higher than in those with rheumatoid episcleritis ($P=0.005$). A similar significant difference was found for patients with non-rheumatoid scleritis, in whom the mean value for haemoglobin was 98.4 per cent, compared with patients with rheumatoid scleritis ($P=0.005$). Comparison of the rheumatoid episcleritis/scleritis group with rheumatoid controls suggested that the anaemia might be more severe in patients with eye inflammation (84.3 to 90.1 per cent) but the difference is not statistically significant for these numbers.

For the purposes of comparison ESR readings for both men and women are grouped together. The ESR in rheumatoid inflammation was very much higher than that in patients with non-rheumatoid episcleritis or scleritis. Unfortunately the methods differed in the two groups. The Westergren method was used at the Centre for Rheumatic Diseases and the Wintrobe method at the Tennent Institute. There is, however, an obvious difference in severity which does not require exact comparison. The mean value in rheumatoid episcleritis was 74.4 mm/1st hour and in rheumatoid scleritis 65.3 mm/1st hour (Westergren). Patients with non-rheumatoid episcleritis

had a mean value of 13.3 mm/1st hour and those with non-rheumatoid scleritis gave a mean value of 19.9 mm/1st hour (Wintrobe). The ESR in rheumatoid episcleritis/scleritis patients was higher than in the rheumatoid control group; mean values were 67.1 mm compared with 48.4 mm. The difference in these values is statistically significant ($P=0.025$).

The mean value of the albumin/globulin ratio in rheumatoid episcleritis was 0.88 while that for rheumatoid scleritis was 1.03. There was a high percentage of reversed ratios in both rheumatoid episcleritis (66.7 per cent) and scleritis (62.2 per cent). Non-rheumatoid patients with episcleritis showed a mean value of 1.75 and those with scleritis a mean value of 1.53. The difference between these two figures is significant ($P=0.05$). Neither of the groups with non-rheumatoid inflammation had any patient with a reversed ratio. There was a highly significant difference between rheumatoid and non-rheumatoid episcleritis ($P=0.001$) and rheumatoid and non-rheumatoid scleritis ($P=0.001$). The mean value of the albumin/globulin ratio in the rheumatoid episcleritis/scleritis group (1.0) was more abnormal than the group of rheumatoid controls (1.12), but the difference was not statistically significant. Consistent with these findings, the

number of patients with a reversed albumin/globulin ratio was greater in the combined episcleritis/scleritis group (63.0 per cent) than in the rheumatoid control group (47.5 per cent).

None of the mean values in all six groups studied is outside the normal range for alkaline phosphatase of 5-15 King Armstrong units, although it is interesting to note that the mean value for rheumatoid scleritis is at the upper limit of normal, and also that 10 of 37 cases with rheumatoid scleritis (27.0 per cent) had raised readings. Further, it is noteworthy that there is a statistically significant difference between the levels for rheumatoid episcleritis and non-rheumatoid episcleritis ($P=0.001$) and between rheumatoid scleritis and non-rheumatoid scleritis ($P=0.05$).

As with alkaline phosphatase, none of the mean values for serum uric acid levels in the six groups of patients investigated was outside the normal range.

A similar pattern emerged for SGOT and SGPT, where all mean values recorded were within normal limits.

WASSERMANN REACTION; VDRL SLIDE TEST, AND REITER PROTEIN COMPLEMENT-FIXATION TEST

The following data relate only to those patients with eye inflammation, both rheumatoid and non-rheumatoid. Seven of the patients with rheumatoid episcleritis and 28 of the patients with rheumatoid scleritis had these investigations and no patient gave a positive result. All the patients with non-rheumatoid episcleritis and with non-rheumatoid scleritis gave similarly negative results.

ANTISTREPTOLYSIN-O TITRE (ASO); BRUCELLOSIS AND TOXOPLASMOSIS

The following data relate only to those patients with rheumatoid episcleritis and scleritis, and non-rheumatoid episcleritis and scleritis.

One patient with rheumatoid episcleritis (14.3 per cent) had a raised ASO titre at 724 units and six with rheumatoid scleritis (20.7 per cent) had raised titres at 320 units (2), 400 units (2), 500 units, and 640 units. Three patients with non-rheumatoid episcleritis (9.1 per cent) showed raised ASO titres, two readings at 320 units and one at 1280 units. One case of non-rheumatoid scleritis (5.6 per cent) had a raised titre at 320 units. None of the patients with a raised ASO titre had erythema nodosum.

Only one of 28 patients with rheumatoid scleritis (3.5 per cent) had a tentative positive result for brucellosis. The standard agglutination test gave a titre of 1/80 for *Brucella abortus*, but the Coombs' test was negative. Serum was anti-complementary. One patient with non-rheumatoid episcleritis (3.1 per cent) had a positive titre for *Brucella abortus* at 1/160 in both the standard agglutination and Coombs' test. However, the complement-fixation test was negative.

The only group of patients with a percentage incidence of positive toxoplasmosis dye test titres outside the normal adult range, approximately 30-40 per cent (Ludlam, 1972), was the very small group of seven cases with rheumatoid episcleritis in which the percentage was 71.4 per cent (Tables XXa, b). It is interesting to note that 8.6 per cent of the patients with rheumatoid episcleritis or rheumatoid scleritis had a titre of 1/256 or more. The group with non-rheumatoid episcleritis and non-rheumatoid scleritis showed only one in the same range (1/1024), 2.0 per cent. It is probable that in the normal adult population the incidence of antibodies at a titre of 1/256 is not more than 1.0 per cent (Beattie, 1958; Ludlam and Beattie, 1963).

AUTOANTIBODIES (Tables XXIa, b)

The following results refer only to those patients with rheumatoid and non-rheumatoid eye inflam-

Table XXa *Toxoplasma* dye test titres in 35 cases (rheumatoid episcleritis and rheumatoid scleritis)

Disease	Cases	< 1/8	+1/8	+1/16	+1/32	+1/64	+1/128	+1/256	+1/512	+1/1024
Episcleritis	7 (2 unknown)	2	—	1	2	—	1	—	—	1
				Total +	5 (71.4 per cent)					
Scleritis	28 (9 unknown)	15	3	1	6	—	1	1	1	—
				Total +	13 (46.4 per cent)					

Table XXb *Toxoplasmosis* (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Disease	Cases	< 1/8	+1/8	+1/16	+1/32	+1/64	+1/128	+1/256	+1/512	+1/1024
Episcleritis	33	17	5	—	8	2	1	—	—	—
				Total +	16 (48.5 per cent)					
Scleritis	18	12	—	1	1	3	—	—	—	1
				Total +	5 (27.8 per cent)					

Table XXIIa Autoantibodies (rheumatoid episcleritis and rheumatoid scleritis) 46 cases

Autoantibody	Cases (no.)	Episcleritis (9 cases)		
		+	Weakly +	Per-centage
Rheumatoid latex	9	9	0	100
Antinuclear factor	9	2	0	22.2
Thyroglobulin TRC	9	0	0	—
Thyroid microsomal	9	1	0	11.1
Smooth muscle	8 (1 unknown)	1	0	12.5
Salivary duct	9	4	0	44.4
Gastric parietal cell	9	3	0	33.3
Mitochondrial	8 (1 unknown)	0	0	—
Scleritis (37 cases)				
Rheumatoid latex	37	35	1	97.3*
Antinuclear factor	37	8	1	24.3
Thyroglobulin TRC	37	3	0	8.1
Thyroid microsomal	37	4	2	16.2
Smooth muscle	34 (3 unknown)	2	6	23.5
Salivary duct	35 (2 unknown)	5	5	28.6
Gastric parietal cell	37	5	1	16.2
Mitochondrial	34 (3 unknown)	0	0	—

*One case is included in which the Rose-Waaler test was used

Table XXIIb Autoantibodies (non-rheumatoid episcleritis and non-rheumatoid scleritis) 51 cases

Autoantibody	Episcleritis (33 cases)		
	+	Weakly +	Percentage
Rheumatoid latex	0	1	3.0
Antinuclear factor	1	2	9.1
Thyroglobulin TRC	0	1	3.0
Thyroid microsomal	3	1	12.1
Smooth muscle	0	0	—
Salivary duct	0	0	—
Gastric parietal cell	1	4	15.2
Mitochondrial	0	0	—
Scleritis (18 cases)			
Rheumatoid latex	0	6	33.3
Antinuclear factor	4	2	33.3
Thyroglobulin TRC	0	0	—
Thyroid microsomal	1	0	5.6
Smooth muscle	1	1	11.1
Salivary duct	0	0	—
Gastric parietal cell	2	0	11.1
Mitochondrial	0	0	—

mation. Apart from the relatively high incidence of salivary duct antibody in the small group with rheumatoid episcleritis, where a positive result was given in four of nine cases (44.4 per cent), and an apparently high incidence of smooth-muscle antibody in rheumatoid scleritis, where eight of 34 cases were positive (23.5 per cent) (although six of these were only weakly positive) the positive autoantibodies listed in Table XXIIa in patients with rheumatoid episcleritis and rheumatoid scleritis is generally in the range expected for patients with rheumatoid arthritis (see Discussion). The possibly significant finding in the non-rheumatoid patients is the high incidence of a weakly positive

rheumatoid factor in patients with non-rheumatoid scleritis, six of 18 cases (33.3 per cent). Also, six patients had a positive antinuclear factor (33.3 per cent); in two of them this was weakly positive. Three patients had a positive rheumatoid factor together with a positive antinuclear factor. The remaining autoantibody investigations in the non-rheumatoid patients were in the range accepted for a general population (see Discussion).

R₃ TITRE (Table XXII)

Sixteen of the rheumatoid episcleritis/scleritis group (42.1 per cent) had titres of 1/512 or higher compared with eight of the rheumatoid controls (21.6 per cent). The difference was just outside significance for these numbers ($\chi^2=3.6148$).

IC/IA GLOBULIN (HUMAN COMPLEMENT C₃); IMMUNOGLOBULIN IgG, IMMUNOGLOBULIN IgA, AND IMMUNOGLOBULIN IgM (Tables XXIIIa, b)

These data also relate only to those patients with rheumatoid and non-rheumatoid eye inflammation. The mean values for rheumatoid episcleritis and rheumatoid scleritis, and non-rheumatoid episcleritis and non-rheumatoid scleritis, all fall within the normal range for each of these investigations. Tables XXIIIa, b record the occasional readings which do not fall within the normal range. These variants predominated in the investigation of ic/ia globulin, where six patients with rheumatoid episcleritis or rheumatoid scleritis and six patients with non-rheumatoid episcleritis and non-rheumatoid scleritis had depressed levels.

BACTERIOLOGY; VIROLOGY, AND MYCOLOGY

Examination of the conjunctiva for bacteria, viruses, and fungi was carried out only in those patients seen at the Tennent Institute of Ophthalmology.

One patient with non-rheumatoid episcleritis had a coagulase-negative staphylococcus. One patient with rheumatoid scleritis and one patient

Table XXII R₃ titres

Table XXIIIa β lc/ β la globulin and immunoglobulins IgG, IgA, and IgM in rheumatoid episcleritis and rheumatoid scleritis

Globulin or immunoglobulin	Rheumatoid episcleritis					Rheumatoid scleritis								
	Cases (no.)	Mean (mg/100 ml)	SD	SEM	Outside normal		Cases (no.)	Mean (mg/100 ml)	SD	SEM	Outside normal			
					Below	Above					Below	Above		
					Per						Per			
					No.	cent					No.	cent		
βlc/βla globulin	8	126.5	±44.1	±15.6	2	25.0	33	142.3	±36.7	±6.4	4	12.1	2	6.1
Immunoglobulin 1gG	7	1365.7	±546.4	±206.5	—	—	33	1717.3	±790.2	±137.6	1	3.0	2	6.1
1gA	7	391.4	±152.8	±57.8	—	—	33	488.5	±259.3	±45.2	—	3	9.1	
1gM	7	141.7	±57.8	±21.9	—	—	33	193.3	±112.0	±19.5	—	—		

Normal values: β lc/ β la globulin 100–190 mg/100 ml; immunoglobulin IgG 560–2800 mg/100 ml; immunoglobulin IgA 104–845 mg/100 ml; immunoglobulin IgM 54–443 mg/100 ml

Table XXIIIb β lc/ β la globulin and immunoglobulins IgG, IgA and IgM in non-rheumatoid episcleritis and non-rheumatoid scleritis

Globulin or immunoglobulin	Non-rheumatoid episcleritis					Non-rheumatoid scleritis								
	Cases (no.)	Mean (mg/100 ml)	SD	SEM	Outside normal		Cases (no.)	Mean (mg/100 ml)	SD	SEM	Outside normal			
					Below	Above					Below	Above		
Per No.	cent	Per No.	cent											
βlc/βla globulin	29	134.5	±31.9	±5.9	3	10.4	16	148.8	±44.2	±11.0	3	18.8	1	6.3
Immunoglobulin IgG	29	1225.2	±491.7	±91.3	—	—	17	1334.1	±339.4	±82.3	—	—		
IgA	29	341.5	±179.7	±33.4	1	3.4	17	403.2	±253.6	±61.5	1	5.9	1	5.9
IgM	29	169.0	±86.0	±16.0	1	3.4	17	202.3	±109.8	±26.7	—	—	1	5.9

Normal values are given with Table XXIIIa

with non-rheumatoid scleritis was a carrier of *Staphylococcus albus*.

No case in the series had any virus cultured from the conjunctiva.

Two patients with non-rheumatoid episcleritis had fungi isolated from the conjunctiva, in both cases the *Penicillium* species. Two patients with rheumatoid scleritis had fungi present, in one case *Penicillium* and in one *Aspergillus*. One further case with non-rheumatoid scleritis produced a fungus of the *Paecilomyces* species.

MORTALITY (Tables XXIV and XXV)

The following data relate to those patients with rheumatoid episcleritis and rheumatoid scleritis,

Table XXIV Mortality (rheumatoid episcleritis, rheumatoid scleritis and rheumatoid controls) 66 cases

Disease	Cases	Deceased	Percentage
Rheumatoid episcleritis/scleritis	33 (2 unknown)*	15	45.5
Rheumatoid controls	33 (2 unknown)*	6	18.2

Statistical analysis: $\chi^2 = 5.6571$; $P = < 0.025$

*These four patients could not be traced

Table XXV Cause of death and associated disease recorded on death certificates (17 cases)

<i>Rheumatoid episcleritis/ scleritis</i> (11 cases; 4 unknown)			<i>Rheumatoid controls</i> (6 cases)		
	<i>No.</i>	<i>Percentage</i>	<i>No.</i>	<i>Percentage</i>	
Myocardial infarction and congestive cardiac failure	5	45.5	4	66.7	
Peptic ulceration	3	27.3	0		
Cerebrovascular accident	1	9.1	2	33.3	
Bronchopneumonia	1		1	16.7	
Pulmonary embolus	1		1		
Pulmonary oedema	1		0		
Hypertension	1		0		
Aortic stenosis and incompetence	1		0		
Hepatitis	1		0		
'Natural causes'	1		0		
Myeloproliferative disease	0		1		
Renal failure	0		1		
Perforated diverticulum of colon	0		1		
Diabetes (maturity onset)	0		1		

comparing them with the rheumatoid control group, matched for age, sex, and year of presentation.

By February 1974, 15 of 33 known cases of rheumatoid episcleritis or rheumatoid scleritis

Table XXVI Type I allergy (atopy) 23 patients

Age (years)	Sex	Diagnosis	Control	House dust	House dust mite (scratch test)	Grass pollen	Alternaria	Feathers	Aspergillus	Candida albicans	Cat hair	Dog hair
34	Female	Episcleritis	-	-	-	-	-	-	-	-	-	-
40	Female	Scleritis	-	-	-	-	-	-	-	-	-	-
34	Female	Episcleritis	-	-	+	-	-	-	-	-	-	-
37	Female	Episcleritis	-	+	++	-	-	++	-	-	-	-
50	Female	Episcleritis	-	-	-	-	-	-	-	-	-	-
22	Male	Episcleritis	-	++	++	+	-	+	-	-	-	-
76	Female	Scleritis	-	-	-	-	-	-	-	-	-	-
61	Female	Episcleritis	-	-	-	-	-	-	-	-	-	-
35	Female	Episcleritis	-	-	-	-	-	-	-	-	-	-
36	Female	Episcleritis	-	+	++	+++	-	-	-	-	-	-
51	Female	Scleritis	-	+	+	-	-	-	-	-	-	-
46	Male	Episcleritis	-	-	-	-	-	-	-	-	-	-
47	Female	Scleritis	-	-	-	-	-	-	-	-	-	-
67	Female	Episcleritis	-	-	-	-	-	-	-	-	-	-
40	Male	Episcleritis	-	-	-	-	-	-	-	-	-	-
40	Male	Episcleritis	-	-	-	-	-	-	-	-	-	-
21	Male	Episcleritis	-	+	+	-	-	+	-	-	++	-
34	Female	Scleritis	-	-	-	-	-	-	-	-	-	-
49	Female	Episcleritis	-	+	++	-	-	+	-	-	-	-
50	Male	Episcleritis	-	-	+	-	-	-	-	-	-	-
70	Female	Episcleritis	-	-	-	-	-	-	-	+	-	-
43	Male	Scleritis	-	-	-	-	-	-	-	-	-	-
50	Male	Episcleritis	-	-	+	-	-	-	-	-	-	-

(45.5 per cent) had died since examination. The control group of patients by February 1974 gave only six of 33 known cases (18.2 per cent) who were deceased. The difference is statistically significant ($P=0.025$).

The details of cause of death, as recorded on the death certificates of these patients, give the expected high incidence of cardiovascular and respiratory disease. One unexpected feature was the finding that three patients of the rheumatoid episcleritis/scleritis groups (27.3 per cent) died after gastrointestinal haemorrhage.

TYPE I ALLERGY (ATOPY) (Table XXVI)

Skin tests in 23 patients, all with non-rheumatoid eye inflammation, and all but six of them cases of episcleritis, did not suggest that there is an increased incidence of atopic disease in these patients. Of the 23 patients, four had a mild positive reaction to house dust or house dust mite, and five had positive skin tests to more than one antigen. Three of the patients with positive skin tests gave a clear history of either hay fever or asthma; the remaining patients with positive skin tests had no clinical history of type I allergy.

Discussion

OPHTHALMOLOGY

There have been few reports reviewing episcleritis and scleritis; most papers have been on individual cases of interest. Studies by Watson and Lobascher (1965), Sevel (1965), Watson (1966), Sevel (1967),

Lyne and Pitkeathly (1968), Fowler (1970), Jayson and Jones (1971), with follow-up studies by Jones and Jayson (1973), Watson (1974), and Lyne (1974), are the sum total of reviews. The incidence of scleritis in rheumatoid arthritis in the study presented has some similarity with the majority of reports previously documented (Table XXVII). Jayson and Jones (1971) in a group of 142 patients had a notably dissimilar figure and Sevel's estimate of one case of scleritis in 3000 patients with rheumatoid arthritis is much lower than our own conclusions. As with the review of Jayson and Jones (1971) this present series was a prospective study for incidence. The incidence of episcleritis in patients presenting with rheumatoid arthritis has not been documented elsewhere, which is understandable as the condition is relatively uncommon, at least in so far as presentation is concerned. Only seven patients, an average of approximately one for each year of the study, are included in this group.

Table XXVII Scleritis in rheumatoid arthritis

Authors	Date	Patients with		Percentage
		Rheumatoid arthritis	Scleritis	
Smith	1957	465	2	0.4
Bywaters	1964	1000	1-2	0.15
Hart	1964	900	±7	0.8
Richardson	1964	1000	±3	0.3
Sevel	1965 (Estimate)	3000	1	0.03
Jayson and Jones	1971	142	9	6.3
Present study	1976	4210	28	0.67

Reports giving the incidence of rheumatoid arthritis in episcleritis and scleritis (Table XXVIII) are consistent with the findings of this study. It will be interesting to follow up the patients without apparent rheumatoid disease some years hence, particularly in view of the finding of one patient with episcleritis and six with scleritis, each of whom had a weakly positive rheumatoid factor.

A very interesting question posed by Sevel (1966) is whether scleritis has been seen more often in recent years. A histogram of his 43 cases which had presented at the Pathology Department, Institute of Ophthalmology, London, between 1950 and 1964 suggests an increased incidence of scleritis since 1954. Studies in rheumatoid arthritis suggest that the incidence of rheumatoid vasculitis has increased since the advent of treatment with systemic corticosteroids (Ferguson and Slocumb, 1961; Smyth and Gum, 1961), although this view does not have unquestioned acceptance (Schmid, Cooper, Ziff, and McEwen, 1961). It may be that the same vasculitis that is possibly related to systemic corticosteroid treatment, in particular to variations in dosage (Slocumb, 1953), has been instrumental in initiating a greater frequency of scleritis. Systemic corticosteroids were first used in the treatment of rheumatoid arthritis in 1949 (Hench, Kendall, Slocumb, and Polly, 1949) and in the treatment of scleritis in 1951 (Talkov, Colpoys, Davis, Papper, and Fienberg, 1951).

The only reports giving the mean age of patients with scleritis in rheumatoid arthritis are those of Sevel (1966), and Jayson and Jones (1971). The nine patients of Jayson and Jones had a mean age of 56.5 years, which is similar to the figure given here (Table IIIa). Sevel's series of 11 cases with rheumatoid scleritis had a mean age of 64.1 years,

but these were eyes which required enucleation, and so were particularly severe examples. Nine patients in our study with rheumatoid episcleritis gave an almost exactly similar mean age as the patients with rheumatoid scleritis (Table IIIa). Non-rheumatoid inflammation presented a lower mean age, particularly for episcleritis (Table IIIb). Lyne and Pitkeathly (1968) reported a similar picture in 55 cases of episcleritis with men having a mean age of 45 years and women 48 years, but their figures included three cases of rheumatoid arthritis. Their 31 cases of scleritis, including nine cases of rheumatoid arthritis, had a mean age of 49 years for men and 50 years for women. It may be that rheumatoid episcleritis and scleritis tend to affect a slightly older age-group of patients with rheumatoid disease. Two of us (JW and DDM) examined a group of 148 patients with rheumatoid arthritis for evidence of steroid-induced cataract, and their mean age was 52.5 years. The control group of 159 patients with rheumatoid arthritis, who had never been treated with systemic corticosteroids, had a mean age of 49.3 years (Williamson, Paterson, McGavin, Jasani, Boyle, and Doig, 1969). In the progression of the disease the most severe cases affect an even older age-group; this was evident in the pathological series of Sevel (1966). The predominance of women with rheumatoid ocular inflammation (Table IIIc) reflects the higher incidence of women with rheumatoid arthritis, a ratio of 2 or 3:1 (Boyle and Buchanan, 1971), and this agrees with previous studies (Sevel, 1965; Jayson and Jones, 1971). Non-rheumatoid inflammation presents us with an intriguing problem. The report of Lyne and Pitkeathly (1968), with only three cases of rheumatoid arthritis in their 55 cases of episcleritis, supports the evidence of this study that non-rheumatoid episcleritis occurs equally in the sexes (Table III d). If episcleritis is due to immune-complex disease and has a similar basis in this respect to scleritis, as suggested by Jones (1971), why is there such a notable difference in the respective sex ratios? The sex ratio in non-rheumatoid scleritis (Table III d), together with the finding that one-third of these patients had a weakly positive rheumatoid factor (one was a man), gives some concern for the future of these patients.

An unusual connective-tissue disorder seen in the present study, in a 45-year-old man with rheumatoid scleritis, presented with widespread granulomas of orbits, nasal septum, sinuses, and lungs, which had occurred intermittently for more than 10 years. The clinical picture was less severe than that of a true Wegener's disease, and lacked the glomerulonephritis typically present in this disease (Godman and Churg, 1954). A chronic dacryocystitis eventually required dacryocystec-

Table XXVIIIa *Rheumatoid arthritis in scleritis*

Authors	Date	Patients with		Percentage
		Scleritis	Rheumatoid arthritis	
Watson	1966	108	35	32.4
Lyne and Pitkeathly	1968	31	9	29.0
Present study	1976	27	9	33.3

Table XXVIIIb *Rheumatoid arthritis in episcleritis*

Authors	Date	Patients with		Percentage
		Episcleritis	Rheumatoid arthritis	
Watson	1966	117	4	3.4
Lyne and Pitkeathly	1968	55	3	5.5
Present study	1976	35	2	5.7

tomy; histological examination showed no necrotizing vasculitis but did show that finger-tip vasculitis, subcutaneous nodules, and skin ulceration had occurred. This case may fall into the category of a limited form of Wegener's disease, as described by Carrington and Liebow (1966) in 16 patients, nine of whom had pulmonary lesions only. Four similar cases have been reported more recently (Cassan, Coles, and Harrison, 1970). Other connective-tissue disorders found in the non-rheumatoid groups of patients were chronic discoid lupus erythematosus associated with episcleritis, and systemic lupus erythematosus associated with scleritis (one case of each). There is some doubt whether these two conditions are separate entities, although systemic manifestations are rare in the chronic discoid form of lupus erythematosus (Boyle and Buchanan, 1971). Systemic lupus erythematosus has been described previously in two cases of episcleritis by Harvey, Shulman, Tumulty, Conley, and Schoenrich (1954) and in isolated reports by Larson (1961) and Spaeth (1967). Associated scleritis has been reported in two cases (Sevel, 1965; Watson, 1966). No previous paper gives episcleritis as a complication of chronic discoid lupus erythematosus.

In the late nineteenth and early twentieth century, gout was considered to be an important cause of ocular inflammation, but the association in most cases of episcleritis or scleritis is vague and indefinite (Duke-Elder and Leigh, 1965). During this century reports of episcleritis have been recorded by Gilbert (1914), Savin (1938), and McWilliams (1952). In recent years only Watson and Lobascher (1965) reported one case with an episcleritis. Two male patients with gout were seen in the present study; one with non-rheumatoid episcleritis and one with a non-rheumatoid necrotizing scleritis. The necrotizing element developed some weeks after the onset of scleritis, and might have been iatrogenic in origin. The patient had a diffuse scleritis which progressed to develop widespread scleral translucency in the upper half of the anterior sclera. A subconjunctival injection in the upper and lower fornices was followed by an area of necrosis above (Fig. 3). The eye subsequently settled satisfactorily. Subconjunctival injections of atropine have been incriminated in the aetiology of scleritis (Tooker, 1931; Swan and Butler, 1951). Three of the five cases of Swan and Butler had skin sensitivity reactions to atropine.

Erythema nodosum, a condition previously associated with episcleritis (McCarthy, 1961) and reported with scleritis (Watson and Lobascher, 1965) was evident in two women with non-rheumatoid episcleritis, and one woman with non-rheumatoid scleritis. There are many common disorders associated with erythema nodosum, including

streptococcal infection, sarcoidosis, tuberculosis, drug reactions (for example, to sulphonamides), rheumatic fever, gonorrhoea, lymphogranuloma inguinale, and coccidioidomycosis (Fry, 1952). James (1961) could not give any aetiological factor in only 23 of 170 cases of erythema nodosum. He found evidence of sarcoidosis in 126 and infection, usually streptococcal, in 21. None of the three patients in this study had a raised ASO titre or any definite history of the conditions listed. The episcleritis in both cases was 'simple', but the patient with scleritis had a nodular lesion. An anterior uveitis was present in the case of nodular scleritis, and this has been documented previously (Allan, 1901). Duke-Elder and Leigh stated that scleral keratitis was a rarity, citing Palich-Szanto (1959). One of the cases of episcleritis, which was bilateral, had associated bilateral sclerosing keratitis.

It is uncertain why many patients with rheumatoid episcleritis and rheumatoid scleritis had a marked increase in electrocardiographic abnormalities (Table IVa). It is possible that the changes, which include bundle-branch block myocardial infarction, and non-specific S-T wave changes, might have been in part, at least, due to rheumatoid involvement of the heart, but without necropsy it is impossible to differentiate between rheumatoid disease, induced ischaemia, and other causes of ischaemic heart disease (Hart, 1969). Pitkeathly, Howitt, and Lyne (1970) documented three cases of aortic incompetence in patients with scleritis, one of whom had a history of polyarthritis of uncertain origin. They presented the scleritis and aortic incompetence as two manifestations of connective-tissue disease. Both patients had right bundle-branch block; this conduction defect was found in three patients with rheumatoid scleritis. A further case of aortic incompetence associated with rheumatoid scleritis was described by Jones and Jayson (1973) in their follow-up study (Jayson and Jones, 1971). In one male patient in this study with diffuse rheumatoid scleritis aortic stenosis and incompetence were discovered *post mortem*. One with rheumatoid episcleritis had aortic stenosis and one with non-rheumatoid scleritis had aortic incompetence. None of these patients had a history of rheumatic fever. According to Sokoloff (1972) rheumatoid disease may occasionally cause a valvulitis with incompetence (Van Valkenburgh, Georges, and Irby, 1972). Pericarditis has been described in association with rheumatoid arthritis and scleritis (Smolero, 1943; Edstrom and Osterlind, 1948; Jayson and Jones, 1971). Two patients in the present study had clinical evidence of pericarditis; one had rheumatoid scleritis and the other non-rheumatoid episcleritis. Pericarditis is a recognized complication of rheumatoid disease (Harrold, 1968; Bacon and Gibson, 1974) and it

was noted by Bonfiglio and Atwater (1969) that patients with pericarditis more often had severe joint disease. Kirk and Cosh (1969) found that 10 of 100 patients with rheumatoid arthritis had clinical features of pericarditis.

A striking increase in pulmonary complications – such as pleurisy, pneumonitis, pleural effusion, and rheumatoid nodules – was apparent in patients with rheumatoid episcleritis and rheumatoid scleritis (Table IVa). Pleural effusion is a recognized entity in rheumatoid disease (Carr and Mayne, 1962; Walker and Wright, 1967). This complication occurs in severe rheumatoid disease as manifested by the presence of subcutaneous nodules (Boyle and Buchanan, 1971). Pulmonary nodules are themselves not uncommon (Noonan, Taylor, and Engleman, 1963). This significant finding of pulmonary disease in patients with rheumatoid eye inflammation as compared with rheumatoid controls, together with the possibility of greater cardiac involvement, emphasizes the serious nature of extra-articular rheumatoid disease affecting vital structures with the probable final seal of significance in the higher incidence of mortality in patients so affected.

There is an increasing appreciation of the association of ocular inflammation and joint disorders in patients with inflammatory bowel disease. Wright, Lumsden, Luntz, Sevel, and Truelove (1965) found that 11.8 per cent of 144 patients with ulcerative colitis had iritis, and 17.4 per cent had sacro-iliac joint abnormalities. Billson, de Dombal, Watkinson, and Goligher (1967) substantiated the association of eye inflammation and ulcerative colitis, and Jayson, Salmon, and Harrison (1970) found that 50 per cent of patients with ankylosing spondylitis and colitis had an anterior uveitis. Lyne and Pitkeathly (1968) reported two patients with ulcerative colitis associated with scleritis, but without any connective-tissue disorder. Watson (1966) described one case of regional ileitis associated with episcleritis, and Hopkins, Horan, Burton, Clamp, de Dombal, and Goligher (1974) recorded two patients with episcleritis associated with regional ileitis. One patient in the present study with rheumatoid episcleritis had recurrent colitis, and one with rheumatoid scleritis had diverticulosis; both were women. The patient with recurrent colitis had an associated anterior uveitis; the patient with diverticulosis had a particularly severe bilateral scleritis with sclerosing keratitis, anterior uveitis, and secondary glaucoma in one eye. However, while it is reported that patients with ulcerative colitis and uveitis have a threefold increase in peripheral joint disease (Wright and Watkinson, 1965; McEwen, 1968) the arthritis is regarded in most instances as distinct from rheumatoid arthritis. It has been called arthritic ulcerative colitis (Ruhl and Sokoloff,

1965) and colitic arthritis or acute toxic arthritis (Fernandez-Herlihy, 1959). Regional ileitis (Crohn's disease) exhibits the same type of peripheral arthritis (Ferguson, 1972). This form of arthritis was first described by Hench (1935). It begins abruptly and reaches its height of intensity within the first day or so, involving the small joints of hands or feet less often than does rheumatoid arthritis (Wright and Watkinson, 1965).

It has been suggested that peptic ulceration occurs more commonly in rheumatoid arthritis (Atwater, Mongan, Wieche, and Jacox, 1965; Bowen, Mayne, Caine, and Bartholomew, 1960; Meltzer, Bockman, Kanenson, and Cohen, 1958), but both are such common diseases that it is unwise to be dogmatic. Four of our patients with rheumatoid scleritis had peptic ulceration and three of the 11 known to have died since examination had gastrointestinal haemorrhage recorded on their death certificates. If the association is valid, is it caused by a vasculitis or is it a therapeutic consequence of, for example, salicylates? Certainly all three patients who died of gastrointestinal haemorrhage had been receiving salicylates. Against this it is noteworthy that four patients with non-rheumatoid episcleritis, that is without severe disease, also had a history of peptic ulceration.

Skin diseases reported with episcleritis are eczema (Watson and Lobascher, 1965), contact dermatitis and acne rosacea (Watson, 1966), psoriasis, lichen planus, and erythema elevatum diutinum (Lyne and Pitkeathly, 1968); and with scleritis, epidermolysis bullosa dystrophica (Mazza and Panagis, 1967). Erythema nodosum, which has already been discussed, has been associated with both episcleritis and scleritis. Psoriasis was evident in two women in the study, one with rheumatoid scleritis and one with non-rheumatoid episcleritis. There were no secondary eye complications in either of the patients with psoriasis. A further patient with non-rheumatoid episcleritis had a history of pityriasis rosea.

Reviewing the literature of scleritis in rheumatoid arthritis, Sevel (1966) found that the condition was more often bilateral. The ratio of 2:1 agrees with the findings given here (Table IIIe). In his own series of 11 enucleated eyes, the disease was unilateral in eight, an inconsistency which Sevel was unable to explain. Extra-articular manifestations of rheumatoid disease are significantly apparent in this present study and the fact that in most cases rheumatoid scleritis is bilateral reflects the widespread nature of extra-articular involvement. Non-rheumatoid scleritis was more often unilateral and whether or not these patients will later develop autoimmune disease, it seems that they have a more localized disorder. Non-rheumatoid episcleritis in contrast was more often bilateral

(Table III*f*) and characteristically recurrent, with inflammation alternating from one eye to the other.

It is generally recognized that the symptoms of episcleritis are less distressing than those of scleritis (Watson and Lobascher, 1965; Jayson and Jones, 1971). One of the objects of this presentation was to provide evidence that these accepted differences do exist. Ocular pain was more apparent in scleritis. The patients complained of a red eye more often in both rheumatoid and non-rheumatoid episcleritis than did those with scleritis (Tables Va, b). A distinctive finding was the higher incidence of complaints of redness and pain in non-rheumatoid inflammation. Perhaps the rheumatoid patient suffers to such a degree elsewhere that the spontaneous complaint of a red and painful eye is not always given. However, Jones and Jayson (1973) pointed out that the fewer complaints in patients with rheumatoid eye inflammation might be due to the many anti-inflammatory drugs which these patients were receiving, or possibly the higher pain threshold which has been described in rheumatoid arthritis (Huskinson and Hart, 1972). In his early description of 'scleritis', Mackenzie (1830) reported that a number of patients described their eyes as hot and dry at the onset of an episode of inflammation. It was interesting to discover a few patients in this study who said that a dry, gritty, or burning eye would often precede the flare-up of inflammation.

It was surprising to find that the history of eye inflammation was slightly longer in the non-rheumatoid group of patients, both for episcleritis and scleritis (Table VI*b*). A simple explanation might be the problem of recollection. Many patients were examined early in the disease, but not all. With so many physical disabilities in what is generally severe rheumatoid disease, the rheumatoid patient might simply have misjudged how long the eye trouble had lasted. Lyne and Pitkeathly (1968) gave a mean duration for all forms of episcleritis of 20 months and a mean duration for all forms of scleritis of 60 months. The difficulty is knowing when an eye is truly quiet and will remain so. Many patients in this study had quiescent periods between inflammation lasting many months, and in one case seven years. Nevertheless, a rather uneasy impression given by the rheumatoid patients is of the disease 'burning out' after two or three years.

As expected, the deeper inflammation of scleritis has a more significant effect on visual acuity (Table VII). The study of visual acuity was confined to patients presenting at the Tennent Institute of Ophthalmology as cases of episcleritis or scleritis, and did not include patients presenting with rheumatoid arthritis at the Centre for Rheumatic Diseases. Visual acuity in these patients was

affected mainly by anterior segment disease, particularly corneal inflammation and cataract. The review of posterior subcapsular cataract/advanced cataract in rheumatoid patients with scleritis who were receiving systemic corticosteroids also suggests, although without supporting figures, a severe effect on visual acuity (Table XII). Furthermore, the group of patients with rheumatoid scleritis who had a posterior segment abnormality would have some disturbance of vision (Table XIII*a*). Fortunately, a cataract can readily be extracted and this should provide some reassurance to the clinician who considers that treatment with systemic corticosteroids is imperative. The male patient who developed gout, and subsequently scleritis, recorded a visual acuity which dropped from 6/6-2 to 6/18-1 in four weeks, due to the development of a variable myopic astigmatism. This eventually settled coincident with quiescence of his scleritis as a mixed astigmatism which, on refraction, gave a visual acuity of 6/5, a reminder that reduction in vision might have had a very simple solution.

The abundance of terms used to describe episcleritis and scleritis requires a new simplicity of approach, and this was provided by the classification of Watson, Hayreh, and Awdry (1968*a, b*), which was used in this study (Tables VIII*a, b*). Clearly the pathological activity in scleritis and nodular episcleritis has the same basis (Manschot, 1961; Sevel, 1967), and it only remains to give a description of the appearance of any inflammation. There has been much confusion regarding the terms 'scleromalacia' and 'scleromalacia perforans' (Van der Hoeve, 1934). 'Scleromalacia' is often used for a diffuse scleritis with scleral translucency, but this is not the eye which is the most likely to perforate, and so confusion results. According to the literature the eye which commonly perforates has a typically necrotizing sclera, and the inflammation is necrotic and the sclera opaque but not translucent (Fig. 3). Most reports of scleromalacia perforans give a distinct destructive picture to the scleral lesion, describing such features as necrosis, sloughing, or ulceration (Van der Hoeve, 1934; Oast, 1937; Verhoeff and King, 1938; Harbater, 1949; Shanedling, 1950; François, 1951; Talkov and others, 1951; Ashton and Hobbs, 1952; Renard, Lelièvre, and Mazel, 1953; Ellis and Holtz, 1953; Armstrong and McGovern, 1955; Marquard, 1956; Boberg-Ans, 1958; Williams and Rosenthal, 1959; Taffet and Carter, 1961; François, Victoria-Troncoso, Hanssens, and Bakskulin, 1969; Gombos, 1967). Blum and Salmoun (1963) and Merz (1964) reported cases where scleral translucency with alarming progressive ectasia necessitated surgical intervention. In these cases there was no necrosis or ulceration.

The importance of these observations is the

appreciation that areas of scleral translucency only rarely give cause for concern. Rheumatoid nodule of the sclera was the term used by Ashton and Hobbs (1952) to describe the scleritis found in rheumatoid arthritis. It gives an accurate description of the granulomatous reaction, similar to that found in the subcutaneous nodule of rheumatoid arthritis. However, a sub-division of the lesions into nodular, diffuse, or necrotizing scleritis provides a clear and simple picture of the scleral reaction with the premise that the inflammation is granulomatous. The overall descriptive term for scleritis which satisfies the pathological uniformity of the condition is necrogranulomatous scleritis (Sevel, 1967). It is interesting that none of our cases of rheumatoid episcleritis was nodular in character, whereas in non-rheumatoid episcleritis nearly one-fifth of cases were nodular (Tables VIIIa, b). Two cases of rheumatoid inflammation initially diagnosed as nodular episcleritis both progressed to a scleritis. Only one patient in the study presented with a necrotizing scleritis. A 63-year-old man developed a non-rheumatoid gouty scleritis, but the necrotizing lesion discussed earlier was probably induced by a subconjunctival steroid injection. Duke-Elder and Leigh (1965) described the possibility of recurrent nodular episcleritis causing the circumcorneal region of the sclera eventually to become slate-coloured. We submit that any appearance of this nature is due to involvement of the sclera and is no longer an episcleritis but a scleritis. The two patients diagnosed initially as having nodular rheumatoid episcleritis subsequently had a distinct slate-coloured zone at the site of inflammation, and were therefore cases of scleritis.

Transparency of the sclera which may accompany scleritis is often described as scleral thinning. This description may create apprehension in the mind of the clinician, and a term such as scleral translucency is preferable. In a recent presentation involving one of us (DDMM), ultrasonographic assessment of the thickness of areas of post-scleritic scleral translucency showed that these areas were not invariably associated with thinning. Only three of eight patients had distinct evidence of thinning of sclera (Rooney, McGavin, Sutherland, and Railton, 1974). The presence of translucency of the sclera reflects the depth and extent of the scleral inflammation, which in this study was very much more evident in rheumatoid scleritis, indicating that scleritis in rheumatoid disease is generally more severe (Tables VIIIa, b). Posterior scleritis is more common in patients with rheumatoid arthritis which also suggests a more extensive inflammation in rheumatoid disease. Inflammation of the posterior sclera is deduced from its secondary effects on neighbouring tissues. Posterior inflammation resulted in choroiditis in two patients, retinal detach-

ment in one, and extraocular muscle imbalance in five. In a paper on the clinical manifestations of scleritis, Watson (1974) found that of 217 eyes with episcleritis, 170 had the simple variety and 47 had nodular episcleritis. Of 301 eyes with scleritis, 119 had diffuse anterior scleritis, 134 had nodular anterior scleritis, 42 showed necrotizing scleritis, and six revealed features of a posterior scleritis. This series, easily the largest general study of episcleritis and scleritis, is particularly significant for its record of the clinical features of these conditions.

Lyne and Pitkeathly (1968) noted that single attacks of episcleritis affected the interpalpebral area in 25 of 33 cases. This distribution of inflammation is substantiated by the present study (Tables IXa, b). Lyne and Pitkeathly suggested that minor trauma might account for this distribution and found a foreign body in one case. Certainly external factors would seem to play a part, whether trauma or some other factor or factors. Patients sometimes complain of a dry, gritty, and burning eye and epiphora was seldom a problem. An eye which is inflamed primarily deep to the conjunctiva may slightly increase in temperature. Evaporation of tears may ensue more rapidly in consequence and so irritation due to exposure will affect the interpalpebral area preferentially. However, this could account only for aggravation of an already inflamed area. It was thought that type I allergy (atopy) might play a part in the external aggravation of an episcleritis. However, in the present study no increase in atopic disease could be found in 23 patients with non-rheumatoid eye inflammation, 17 of whom had episcleritis. Inflammation affecting the anterior sclera in rheumatoid arthritis affects the upper half of the sclera more often than the lower half (Jayson and Jones, 1971), and Sevel's review of the literature confirms this view. Sevel (1965) in his 11 cases examined histologically, found that 18.0 per cent had disease of the posterior segment, and his investigation of the literature with regard to eyes enucleated because of scleritis gave a figure of 12.0 per cent. These figures are not dissimilar to our own for rheumatoid scleritis (Table VIIIa). However, the distribution of anterior scleritis in this report, although more often affecting the superior aspect of the sclera, does not have the considerable emphasis of Sevel's cases (Table IXa). Jayson and Jones (1971) in their group of 14 patients found a distribution similar to that seen in our study.

Corneal complications in scleral inflammation have been described for over a century (Mackenzie, 1830). The predominant disturbance is a sclerosing keratitis which, according to Watson, Hayreh, and Awdry (1968a), occurs in nearly half of those patients with scleritis but seldom in those with

episcleritis. In 11 cases which were enucleated and comprised the series of rheumatoid scleritis (Sevel, 1965), 36.0 per cent had some form of keratitis. However, rheumatoid episcleritis and rheumatoid scleritis in this investigation showed a high incidence of corneal complications (Table Xa), in particular sclerosing keratitis (Fig. 4), and it was interesting to find that anterior uveitis although less common had a similar incidence in rheumatoid episcleritis and rheumatoid scleritis, unexpected findings as regards episcleritis. The anticipated difference between episcleritis and scleritis was confirmed in regard to cataract, glaucoma, and posterior segment disease, but it will be recalled that only 13 eyes had rheumatoid episcleritis. Corneal ulceration occurred in two forms; limbal guttering (Fig. 5), which has been called marginal furrows (Brown and Grayson, 1968), and keratolysis. While limbal guttering may persist for a considerable time, and during the active phase of scleral inflammation appears to 'creep' around the limbus, keratolysis is a more dramatic 'melting' of the cornea which may result in loss of the anterior chamber with iris prolapse. Watson and Holt-Wilson (1974) described a further corneal complication of scleritis which they called deep keratitis, in which a deep sheet opacity with deep vascularization after long-standing recurrent scleritis was evident. We have recently seen a young woman with non-rheumatoid scleritis, who is not included in this study, where this striking corneal complication was present.

The main feature of interest in the patients with anterior uveitis was the higher incidence of posterior synechiae in patients with rheumatoid scleritis as compared with non-rheumatoid scleritis. This would suggest a more active and tenacious form of uveal inflammation, which is consistent with the impression of severe ocular disease in rheumatoid arthritis. However, the presence of anterior uveitis in both rheumatoid and non-rheumatoid inflammation was very nearly as common in episcleritis as in scleritis. Anterior uveitis occurred in approximately one-fifth of patients with episcleritis and it occurred in about one-quarter of those with scleritis (Tables XIa, b). Iridocyclitis has often been described with scleritis (Wolfe, 1882; Kiehle, 1946; Duke-Elder and Leigh, 1965). Sevel (1965) in his series of 11 rheumatoid cases found histological evidence of cyclitis in 46.0 per cent. The figures given in this study are objective in that they indicate evidence of active or old uveitis (for example, posterior synechiae), and so the true figure will be higher. A deep scleritis will invariably be accompanied by uveitis—whether iritis, cyclitis, or choroiditis—but a number of cases, particularly in the anterior segment, may settle without any residual evidence of inflammation.

Posterior subcapsular cataracts have been re-

ported in 10.5 to 60 per cent of patients with rheumatoid arthritis receiving treatment with long-term oral corticosteroid therapy (Black, Oglesby, von Sallmann, and Bunim, 1960; Giles, Mason, Duff, and McLean, 1962; Crews, 1963; Irby, Toone, Wittkamp, and Wiesinger, 1964; Spencer and Andelman, 1965; Furst, Smiley, and Ansell, 1966). A similar study at the Centre for Rheumatic Diseases, Glasgow, provided an incidence of steroid-induced cataract of 11.5 per cent (Williamson and others, 1969). The combination of treatment with systemic corticosteroids and the presence of anterior segment inflammation in the form of scleritis carries a high risk of the development of cataract; in this study, an incidence of 36.0 per cent (Table XII). While it is helpful to be aware of this possible complication, it is reassuring that where systemic corticosteroid treatment is clearly indicated, any resulting cataract can be removed by surgery.

Posterior scleritis can provoke various intraocular side-effects including choroiditis with exudative retinal detachment (Radnót, 1948; Harper, 1960; Hurd, Snyder, and Ziff, 1970), macular oedema (Watson and Lobascher, 1965), retinal striations (Sears, 1964) and optic disc oedema (Bertelsen, 1960). Orbital myositis is an extraocular manifestation (Gorduren, 1962; Maria, 1956). In his pathological series, Sevel (1965) found choroiditis (64.0 per cent), choroidoretinitis (9.0 per cent) and retinal detachment (64.0 per cent). Rheumatoid scleritis provides disturbing indications of deep-seated inflammation, posterior segment abnormality affecting nearly one-third of the patients (Table XIIIa). Although macular disturbance could have other causes, such as drug-induced maculopathy, senile degeneration (Bedell, 1950; Favre, 1960) and vascular disease (Norn, 1961) it is recognized that it may occur with retinitis (Manschot and Von Wining, 1953) or iridocyclitis (Samuels, 1930; Wolff, 1931). It is possible, therefore, that the large number of rheumatoid patients with a macular disturbance may be attributed, in part at least, to the consequence of severe scleritis, the incidence being higher than in the non-rheumatoid patients with scleritis, both groups having a mean age in the sixth decade. The uveitis accompanying a scleritis is more often an anterior uveitis, but whether anterior or posterior it is from this serious complication that most of the consequent ocular problems arise, problems which affect vision—such as cataract, glaucoma, exudative retinal detachment, and macular disturbance. Optic nerve disease after scleritis has had little documentation. Bertelsen (1960) described 12 patients with a posterior scleritis and two of these had oedema of the optic nerve head. The cases of Gorduren (1962) and Maria (1956) of scleritonitis and

orbital myositis both had optic nerve oedema with associated retinal oedema. One patient in the present series with a rheumatoid scleritis had optic disc oedema.

Watson (1966) found that seven of 108 cases with scleritis (6.5 per cent) had raised intraocular pressure, and Sevel (1965) in his study of enucleated eyes reported that 45.0 per cent of 43 cases had a history of secondary glaucoma. Watson's cases settled with the good response of the scleritis to systemic treatment. He stated that surgery was avoided because of the dangers of aggravating the inflammation. Apart from one case of non-rheumatoid episcleritis with an intraocular pressure fractionally above the upper limit of the normal range, all cases of secondary glaucoma in this study were in patients with scleritis (Tables XIVa, b). As in Watson's series (1966), the intraocular pressure settled coincident with quietening of the scleritis in most cases. One patient required surgery and one patient, with a minimally raised pressure (22 mmHg), is still receiving medical treatment. If the indications for operative intervention become compelling, surgery should be carried out despite the presence of inflammation. The patient with rheumatoid arthritis and severe scleritis who required surgery underwent a drainage procedure without any exacerbation of inflammation.

The deeper and more extensive inflammation of scleritis affects ocular movement considerably more often than episcleritis, and one suspects that the latter may affect movement only because of the discomfort sustained in moving the eye to the affected side (Tables XVa, b). There is a close association of scleritis, in particular posterior scleritis, with tenonitis, myositis, and pseudotumour formation. (Although orbital myositis has been called a form of pseudotumour the differentiation in terms seems more appropriate.) It is sometimes difficult to reach the correct diagnosis in these conditions. The patient presents with pain, limitation of ocular movement, chemosis, and sometimes lid oedema. The indirect consequence of inflammation provides the clue to diagnosis, and this appearance will often simulate orbital cellulitis. Bertelsen (1960) confesses to this mistake in six of his 12 patients with sclerotonitis and orbital myositis. Both Gorduren (1962) and Maria (1956) began treatment with systemic antibiotics in their cases before reaching the true diagnosis. Coop (1961) in a series of 47 cases of orbital pseudotumour found nine which presented with chemosis as part of the clinical picture. In the woman with non-rheumatoid scleritis who presented with strabismus there was the same confusion in diagnosis. A biopsy of the central strip of tendon/muscle of the lateral rectus muscle confirmed the diagnosis. There was no untoward effect on the

inflammation as a result of surgical intervention.

The incidence of Sjögren's syndrome in rheumatoid arthritis has been estimated at between 9 and 34 per cent, and in the sicca syndrome there is a 60 to 75 per cent incidence of connective-tissue disease (Henkind and Gold, 1973). Talal (1972) considers that keratoconjunctivitis sicca develops in 10 to 15 per cent of patients with rheumatoid arthritis and cites the report of Stenstam (1947). While the incidence of keratoconjunctivitis sicca in the present study in patients with rheumatoid episcleritis and rheumatoid scleritis falls within the accepted range for rheumatoid arthritis, the incidence of Sjögren's syndrome is considerably higher than that found by Williamson (1970) in patients with rheumatoid arthritis, also attending the Centre for Rheumatic Diseases. He found that between 6 and 7 per cent of patients with rheumatoid arthritis had Sjögren's syndrome. The incidence given here in rheumatoid episcleritis (33.3 per cent) and rheumatoid scleritis (32.4 per cent) reflects the extent of extra-articular manifestations in patients with rheumatoid episcleral and scleral inflammation.

RHEUMATOLOGY

It is not the purpose of this paper to discuss the rheumatological findings in any detail. However, some of the results of this aspect of our study lead us to suspect that the underlying disease of scleritis in these patients may be a vasculitis.

The arthritis in patients with rheumatoid episcleritis and rheumatoid scleritis was of longer duration and revealed more severe erosive changes on x-ray examination as compared with the rheumatoid controls (Table XVII). On the other hand, the functional capacity and the degree of joint tenderness were similar in the rheumatoid patients with and without inflammatory eye disease. Subcutaneous nodules in rheumatoid arthritis are found in approximately one-third of patients (Boyle and Buchanan, 1971). Of the patients with rheumatoid episcleritis and rheumatoid scleritis 50 per cent had subcutaneous nodules, twice the percentage found in the control group of patients (Table XVIII). Histological studies of early nodule formation by Sikoloff, McCluskey, and Bunim (1953) suggest that the nodule develops around an inflamed blood vessel. It is significant that biopsy of episcleral nodules in patients with rheumatoid arthritis has given a pathological picture similar to that of the subcutaneous nodule of rheumatoid arthritis (Edstrom and Osterlind, 1948; Mundy, Howard, Stillman, and Bevans, 1951; Ferry, 1969), and examination of enucleated eyes with scleritis has confirmed a uniform basic pathology (Manschot, 1961; Sevel, 1965).

Approximately 25 per cent of patients with rheumatoid arthritis have vasculitis on *post-mortem* examination (Cruickshank, 1954). Rheumatoid vasculitis, unlike classical polyarteritis nodosa, spares the kidneys, and hypertension and asthma are rare (Ferguson and Slocumb, 1961). It is interesting that while respiratory disease and possibly cardiac involvement were features notable in the patients with rheumatoid eye inflammation, renal disease was not a problem. Rheumatoid vasculitis affects the peripheral nerves (Hart, Golding, and McKenzie, 1957; Ferguson and Slocumb, 1961; Wilkinson and Torrance, 1967), giving rise to a sensory and/or motor neuropathy (Hart and Golding, 1960; Schmid and others, 1961) and to dermal infarction (Bywaters, 1957; Golding, Hamilton, and Gill, 1965). In the group of patients with rheumatoid episcleritis and rheumatoid scleritis, 8.9 per cent had a peripheral neuropathy, presumably due to vasculitis affecting the vasa nervorum, and 13.3 per cent had skin ulcers, both incidences very much higher than expected, although for these numbers there was no statistically significant increase in the incidence of peripheral neuropathy or skin ulcers as compared with that in rheumatoid controls (Table XVIII).

Many patients with rheumatoid scleritis also manifested skin bruising and skin atrophy (Table XVIII), features almost certainly attributable to systemic corticosteroid treatment, which most of the patients were receiving (Boyle and Buchanan, 1971). It has been suggested that systemic corticosteroids produce alteration in the dermal connective tissue, particularly in collagen (Scarborough and Schuster, 1960; Greenwood, 1966).

Patients with rheumatoid ocular inflammation also had a high incidence of splenomegaly (10.9 per cent) (Table XVIII). All five patients with splenomegaly had anaemia and two of the patients had a neutropenia. The syndrome of chronic rheumatoid arthritis, splenomegaly, and neutropenia, first described by Felty (1924), is said to occur in fewer than 5 per cent of patients with rheumatoid arthritis (Walker and Wright, 1968).

The picture that emerges in the patient with rheumatoid episcleritis and rheumatoid scleritis is that of long-standing rheumatoid disease and severe erosive joint changes on x-ray examination, with many extra-articular manifestations of rheumatoid disease, many of which reflect an underlying rheumatoid vasculitis. Episcleritis and scleritis in these patients is further evidence of widespread and severe disease affecting eyes, peripheral nerves, skin, lungs, and possibly the heart. These findings substantiate the reports of Jones and Jayson (1973), who found a significant incidence of rheumatoid subcutaneous nodules and other features of microvasculitis in patients with rheumatoid scleritis.

LABORATORY INVESTIGATIONS

Laboratory data confirm the expected evidence of widespread disorder in patients with rheumatoid disease as compared with patients with non-rheumatoid eye inflammation. A significant difference was noted in the findings comparing rheumatoid and non-rheumatoid patients as regards haemoglobin and albumin/globulin ratio. The erythrocyte sedimentation rate was measured by two different methods but the readings in patients with rheumatoid disease were clearly far higher (Tables XIXa, b). It is interesting to note that the mean values for haemoglobin, erythrocyte sedimentation rate, and albumin/globulin ratio were all more abnormal in the patients with rheumatoid episcleritis and rheumatoid scleritis than in the rheumatoid control group, although only the findings for the erythrocyte sedimentation rate were statistically significant (Table XIXc).

The normal adult range for positive titres to *Toxoplasma gondii* is in the region of 30 to 40 per cent. Only the small group of patients with rheumatoid episcleritis had a figure that was very much higher (Table XXa). Beattie (1958) found 0.2 per cent of normal adults with a titre of 1/256 or more and Ludlam and Beattie (1963) reported only one titre at 1/512 in 478 women (0.2 per cent). In the patients with rheumatoid eye inflammation three of 35 patients (8.6 per cent) had titres of 1/256 or more. A similar increased incidence of high titres, noted in this paper in patients with rheumatoid eye inflammation, has been recorded in primary biliary cirrhosis (MacSween, 1973), reticulosis or after immunosuppressive or antimetabolite treatment (Broughton, 1970), pregnancy (Purtilo, Hallgren, and Yunis, 1972) and where a choroidoretinitis due to toxoplasmosis may relapse and toxoplasma antibody levels rise (Beattie, 1958). These are conditions associated with impaired cell-mediated immunity, and there is recent evidence of depression of cell-mediated immunity in some patients with rheumatoid arthritis (Waxman, Lockshin, Schnapp, and Doneson, 1973).

The titre of rheumatoid factor reflects the severity of the disease (Ziff, 1957; Kellgren and Ball, 1959) and the consequent prognosis (Duthie, Brown, Truelove, Barager, and Lawrie, 1964). It is not surprising, therefore, that some patients with rheumatoid episcleral or scleral inflammation had relatively high titres (Table XXII). Higher titres of rheumatoid factor are also associated with many extra-articular manifestations of rheumatoid disease such as subcutaneous nodules (Kellgren and Ball, 1959), vasculitis, peripheral neuropathy, and intractable skin ulcers (Epstein and Engleman, 1959). Autoantibody investigations in rheumatoid episcleritis and rheumatoid scleritis generally show

results consistent with the expected incidence in a general rheumatoid population (Table XXIa). In tests of patients with rheumatoid arthritis, Pollak (1964) found that 24 per cent had positive antinuclear results, and Weir, Holborow, and Johnson (1961) found that 14 per cent were similarly positive. Thyroid antibodies in patients with rheumatoid eye inflammation showed no striking increase and indeed did not match the incidence of 15 of 62 cases (24.2 per cent) of rheumatoid arthritis found by Anderson, Goudie, Gray, and Buchanan (1961). The incidence of thyroid microsomal antibody in the present study of rheumatoid patients with eye inflammation is only slightly lower than that in the female group reported by Buchanan, Crooks, Alexander, Koutras, Wayne, and Gray (1961), where 26.1 per cent of 46 women had thyroid microsomal antibody. Johnson, Holborow, and Glynn (1965) found an incidence of smooth-muscle antibody in 6.4 per cent of 47 patients with rheumatoid arthritis and Doniach, Roitt, Walker, and Sherlock (1966) an incidence of 16 per cent in 32 patients with rheumatoid arthritis. The figure given here in rheumatoid scleritis (23.5 per cent) is slightly higher than in these two series, but it is difficult to reach any conclusion at this stage regarding this finding. High incidences of smooth-muscle antibody have been found in liver disease, particularly active chronic hepatitis (67 per cent), primary biliary cirrhosis (50 per cent), and cryptogenic cirrhosis (28 per cent) (Doniach and others, 1966). Certainly liver disease has been noted in association with rheumatoid arthritis, but the incidence was small; 0.66 per cent of patients with rheumatoid arthritis alone and 1.5 per cent of patients with Sjögren's syndrome, in whom the connective-tissue disorder was rheumatoid arthritis (Whaley and others, 1970). Salivary duct antibody was found in one-quarter of patients with rheumatoid arthritis, apparently uncomplicated by Sjögren's syndrome (MacSween, Goudie, Anderson, Armstrong, Murray, Mason, Jasani, Boyle, Buchanan, and Williamson, 1967), and it would appear that the present findings are consistent with their observations without drawing any conclusion from the higher percentage of antibodies in the very small group with rheumatoid episcleritis. Armstrong (1967) considered that there was no evidence that gastric parietal-cell antibodies occurred more commonly in rheumatoid arthritis. In his investigation of patients with rheumatoid arthritis, 16.2 per cent of 246 females and 6.3 per cent of 79 males had positive results for gastric parietal-cell antibody. The small group of patients with rheumatoid episcleritis precludes any accurate conclusion and the group of patients with rheumatoid scleritis had a percentage incidence of gastric parietal-cell antibody of 16.2 per cent.

The results of the autoantibody tests in patients with episcleritis and scleritis, but with no clinical or radiological evidence of rheumatoid arthritis, are of particular interest (Table XXIb). One-third of the patients with scleritis gave positive results to tests for rheumatoid factor, and this might be an early manifestation of rheumatoid disease. Alternatively, it is conceivable that plasma cells in the scleral infiltrate could produce rheumatoid factor. It is known that plasma cells in the lymphoid tissues and in lymphoid infiltrates of synovium induce rheumatoid factor which then circulates in the blood stream (Mellors, Nowoslawski, and Korngold, 1961). It is possible, therefore, that the low titre of rheumatoid factor in the blood of those patients with scleritis, but no rheumatoid arthritis, merely reflects local scleral inflammation. However, only careful long-term follow-up studies will answer this question. The incidence of antinuclear factor in the serum of patients with non-rheumatoid scleritis could also indicate potential systemic disorder. Previous studies give a lower figure for the presence of antinuclear factor in the serum of patients with rheumatoid arthritis (14 per cent: Weir and others, 1961; 24 per cent: Pollak, 1964) and it is known that the prevalence and titre of antinuclear factor is highest in patients with severe arthritis (Hall, Bardawil, Bayles, Mednis, and Galins, 1960), vascular and granulomatous complications and Felty's syndrome (Alexander, Bremner, and Duthie, 1960; Ward, Johnson, and Holborow, 1964). Thyroglobulin antibody in patients with non-rheumatoid episcleritis and non-rheumatoid scleritis shows no increase beyond figures previously recorded for normal populations (5 per cent: Roitt and Doniach, 1958; 6 per cent: Owen and Smart, 1958; 4 per cent: Blizzard, Hamwi, Skillman, and Wheeler, 1959; 10 per cent: Beutner and Witebsky, 1962). Similarly, the incidence of thyroid microsomal antibodies is similar to the figure of 8 per cent given by Beutner and Witebsky (1962) for a normal population. Other autoantibody tests in patients with non-rheumatoid eye inflammation show little variation from general population studies for smooth-muscle antibody (13.5 per cent: MacSween, 1973) and gastric parietal-cell antibody, in which a general population study of hospital inpatients older than 50 years gave a figure of 10 per cent with the higher figure of 13.6 per cent in women (Anderson, Buchanan, and Goudie, 1967). MacSween (1973) in his group of 114 control patients in a study of primary biliary cirrhosis found an incidence of 10 per cent in women and 5 per cent in men.

The complement system consists of a group of serum proteins which amplify the effects of some antigen-antibody interactions (Austen, 1972). In rheumatoid arthritis, serum complement levels

have been found to be normal or slightly raised (Ellis and Felix-Davies, 1959) and also reduced (Mongan, Cass, Jacox, and Vaughan, 1969; Weinstein, Peters, Brown, and Bluestone, 1972). Six rheumatoid patients in this study show reduced values (Table XXIIIa) and it may be that hypo-complementaemia reflects active vasculitis, as has been shown previously in rheumatoid arthritis (Mongan, Cass, Jacox, and Vaughan, 1969; Weinstein and others, 1972). Six of the patients with non-rheumatoid eye inflammation also had serum complement levels below 100 mg/100 ml (Table XXIIIb) and it is difficult to suggest causes of this finding. One of these patients gave a history of gout and essential hypertension, and another had erythema nodosa. However, it should be noted that there is some dubiety as to what is the range of normal for serum complement readings. The normal mean value in this study was taken as 145 mg/100 ml (± 22 mg/100 ml) (Shanbrom, Khoo, and Lou, 1967). Thompson (1972) found a mean value of 118 mg/100 ml (± 26 mg/100 ml) in 66 healthy individuals.

Immunoglobulins IgG, IgA, and IgM show little variation from normal figures in either rheumatoid or non-rheumatoid eye inflammation.

MORTALITY

The mortality in rheumatoid patients with episcleral and scleral inflammation was soberingly high, 45.5 per cent (Table XXIV). Fifteen of 33 known cases of rheumatoid episcleritis or rheumatoid scleritis had died since examination, compared with six of 33 known rheumatoid control patients (18.2 per cent). A decreased life expectancy has been observed in rheumatoid arthritis (Reah, 1963) and the outlook and severity of the condition is always more grave in sero-positive disease (Duthie and others, 1964). Jones and Jayson (1973) found that five of their original 14 patients with rheumatoid scleritis had died within three years, a mortality of 36 per cent. Only 18.5 per cent of their 133 control patients had died during the same period. The figures for mortality suggest that the conclusion of Decker (1972) was accurate: 'death due solely to rheumatoid arthritis is rare indeed. When it occurs it is due to the extra-articular manifestations'.

TYPE I ALLERGY (ATOPY)

The simplest methods of screening patients for type I allergy are either to carry out a series of skin tests, as has been done here, or to measure the blood levels of IgE. A group of 23 patients, each patient with non-rheumatoid eye inflammation, failed to give any indication on skin testing of a

higher incidence of atopy than would have been expected in the general population. The incidence is within the range found in controls during studies of type I allergy (Johansson, 1967). This finding in a small series suggests that any external factor which might predispose to the interpalpebral distribution of inflammation found in many patients with episcleritis (Lyne and Pitkeathly, 1968) (Table IXb) does not have its origin in a susceptibility to atopic disease.

In a recent publication reviewing ocular manifestations of rheumatic disorders, Henkind and Gold (1973) plead for the inclusion of examination by an ophthalmologist in the protocol for any prospective study of rheumatic disease. This study, which has anticipated their request by some years, attempts to collate the ocular manifestations of episcleritis and scleritis with the rheumatic disorders, in particular rheumatoid arthritis.

Conclusions

1. Episcleritis occurred in approximately two patients per 1000 with rheumatoid arthritis (0.17 per cent). Scleritis occurred in approximately seven patients per 1000 with rheumatoid arthritis (0.67 per cent). Rheumatoid arthritis is common in patients presenting with scleritis, in this series occurring in one-third of patients (33.3 per cent), but is less common in patients presenting with episcleritis, occurring in approximately one patient in 20 (5.7 per cent).
2. All patients with rheumatoid episcleritis, rheumatoid scleritis, and non-rheumatoid scleritis had a mean age in the sixth decade, and the disease was more prevalent in women; whereas patients with non-rheumatoid episcleritis had a mean age in the fifth decade and the disease occurred equally between the sexes.
3. Rheumatoid episcleritis and rheumatoid scleritis were associated with widespread systemic disease, particularly of the cardiovascular and respiratory systems.
4. The most common complaints in episcleritis and scleritis were of redness and pain. Ocular pain was more evident in scleritis. Eye symptoms were more readily noted in non-rheumatoid inflammation.
5. All groups of patients had a very wide range in the duration of intermittent ocular inflammation, from a few days or weeks to 15 years or more.
6. Visual acuity is more severely depressed in scleritis than in episcleritis as a result of the associated ocular complications.
7. In a classification of scleritis as nodular,

diffuse, and necrotizing, diffuse scleritis was the most common form in both rheumatoid and non-rheumatoid scleritic inflammation. Posterior scleritis was more common in rheumatoid scleritis than in non-rheumatoid inflammation. Scleral translucency was found considerably more often in rheumatoid than in non-rheumatoid scleritis.

8. Ocular inflammation in episcleritis usually affected the interpalpebral area. Rheumatoid scleritis had a fairly even distribution in all four quadrants of the anterior sclera.
9. Episcleritis and scleritis associated with rheumatoid disease had more associated ocular complications than episcleritis and scleritis unassociated with rheumatoid disease.
10. Posterior subcapsular cataract was common in rheumatoid scleritis in cases in which the patient had been given systemic corticosteroids, occurring in 36 per cent of these patients.
11. Rheumatoid episcleritis and rheumatoid scleritis generally presented in patients with rheumatoid disease of long duration and in patients with radiological evidence of more advanced joint disease when compared with rheumatoid control patients.
12. Subcutaneous granulomatous nodules and skin atrophy were significantly more common in patients with rheumatoid episcleritis and rheumatoid scleritis when compared with rheumatoid control patients. Although not statistically significant, peripheral neuropathy, skin ulceration, skin bruising, and splenomegaly were all more apparent in patients with rheumatoid episcleritis and rheumatoid scleritis than in the rheumatoid control group.
13. Sjögren's syndrome was more evident in patients with rheumatoid episcleritis and rheumatoid scleritis when compared with general rheumatoid patients also referred to the Centre for Rheumatic Diseases.
14. The erythrocyte sedimentation rate was significantly higher in patients with rheumatoid episcleritis and rheumatoid scleritis when compared with the rheumatoid control patients.
15. Antibodies to *Toxoplasma gondii* in patients with rheumatoid episcleritis and rheumatoid scleritis showed a higher percentage of

raised titres compared with studies in normal patients.

16. Autoantibody studies in patients with rheumatoid episcleritis and with rheumatoid scleritis showed little variation from results expected in rheumatoid arthritis. Autoantibody studies in patients with non-rheumatoid scleritis showed a high incidence of rheumatoid factor (33·3 per cent) and antinuclear factor (33·3 per cent).
17. The prognosis for life is poorer in patients with rheumatoid disease complicated by episcleritis or scleritis when compared with rheumatoid controls matched for age, sex, and year of presentation; 45·5 per cent of those with eye inflammation had died since the examination, compared with 18·2 per cent of the control group.
18. There is no clear evidence of any higher incidence of atopic disease in patients with non-rheumatoid episcleritis and non-rheumatoid scleritis as compared with the expected incidence in a general population.

Many colleagues supported our study, and for this we express our warmest gratitude. A number of ophthalmologists in the west of Scotland took interest in the study and referred patients to the scleritis clinic. Without their help the investigation would have been incomplete. Dr G. B. Ludlam kindly provided data for our study of positive titres for *Toxoplasma gondii*. Mrs Hazel Hughes, Mrs Catriona Breen, and Mrs Mary Mason of the Immunopathology Laboratory, Glasgow, examined sera for autoantibody studies and Miss Tineke Simmes gave us information regarding immunoglobulin estimations. Miss Nancy Wylie of the library, Royal College of Physicians and Surgeons, Glasgow, has been a constant help in obtaining papers and checking references. The illustrations for the paper were from the Department of Medical Illustration, Southern General Hospital (Mr R. Loudon Brown, Mr Robin Ewart, and Mr Alastair Irvine), and from the Tennent Institute of Ophthalmology (Mr John Watt and Mrs Anne Currie). Mr R. Clelland, Registrar of Births, Deaths and Marriages, Glasgow, obtained details of death certificates for patients who had died since examination.

The expenses of the study were supported by two grants, from B.D.H. Pharmaceuticals (£100) and Geigy Pharmaceuticals (£120).

Tables VIII, XII, XVII, XVIII, XXIV, XXVII, XXVIII, are reproduced in whole or in part by kind permission of Churchill Livingstone, Edinburgh.

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