SJÖGREN'S SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS

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For some time there has been evidence that Sjögren's syndrome is a "collagen disease" (Cardell and Gurling, 1954; Ramage and Kinnear, 1956). As the capacity of connective tissue to react to injury is limited to a few basic patterns, probably few "collagen diseases" are worth considering as separate entities. Any evidence demonstrating that what are now thought to be two separate "collagen diseases" are really different forms of the same disease is therefore desirable. In this paper clinical and pathological evidence is produced showing that Sjögren's syndrome may be a chronic and relatively benign form of systemic lupus erythematosus.

Systemic L.E. is a disease of connective tissue characterized by a prolonged intermittent clinical course during which a variety of organ systems may be involved in an episodic manner. Pathologically it is characterized by the presence of the L.E. factor, which is a protein or protein-bound substance present in all the body fluids and exudates and is responsible for the L.E. cell phenomenon and the formation of haematoxyphil bodies.

The most striking feature of Sjögren's syndrome is a diminution or cessation of secretions from the lacrimal and salivary glands and from the submucous glands of the respiratory and upper alimentary tracts; it is often associated with other systemic disturbances, the most common of which is rheumatoid arthritis.

Its pathological features have been well described by Sjögren (1943).

Lacrimal and Salivary Glands.—In the lacrimal glands connective-tissue proliferation and fibrosis are pronounced. Hyaline nodes may form in the glandular parenchyma and there is marked atrophy of the glandular tissue. Considerable round-cell infiltration occurs, chiefly by lymphocytes and plasma cells. The walls of the blood vessels are often thickened by hyaline tissue. Similar changes occur in the salivary glands, including the small glands of the mouth, nose, pharynx, and larynx. In the parotid and probably the other salivary glands lymphoid follicles may develop; these have not been seen in the lacrimal glands.

Conjunctiva.—The bulbar conjunctiva is oedematous in both the epithelial and the subepithelial layers. The epithelial cells become swollen and their nuclei are often enlarged and possess more or less conglomerated chromatin. Marked thinning of the epithelium occurs in the later stages of the disease. In the subepithelial tissue there is early destruction of elastic tissue, and hyalinization of the connective tissue is sometimes very pronounced. Close beneath the epithelium there is infiltration with round cells, mostly plasma cells. The goblet cells, mainly found in the fornices, are very swollen and are present in increased proportions.

Cornea.—The epithelial changes are similar to those of the conjunctiva. In addition, however, in the substantia propria of the cornea and in the sclera small sharply defined areas may be seen. These are generally oval in shape and in unstained preparations show a slight brownish tint. With haematoxylin they stain blue. The exact nature of the change which causes them is not known.

Clinical and Pathological Investigations

I saw 28 consecutive cases of Sjögren's syndrome at the Bristol Eye Hospital in a period of nine months. In each case a history was taken and a physical examination carried out. Urinary albumin, haemoglobin, full blood count, E.S.R., and electrophoresis of the serum proteins were done and the peripheral blood was examined for L.E. cells, using the coagulated blood technique on three occasions at intervals of about three weeks. Tables I and II summarize the salient points of this investigation.

TABLE I.—*Salient Features of 28 Cases of Sjögren's Syndrome*

	No. of Cases
Rheumatoid arthritis	17
Arthralgia	9
Chilblains and/or Raynaud's phenomenon	12
Purpura	7
Photosensitivity	4
Thyroid disease	4
Colitis	2
Hypochromic anaemia	5 out of 27
Leucopenia	5 out of 27
Thrombocytopenia	16 out of 26
Raised E.S.R.	14 out of 26
Lowered albumin	15
Increased α_2- globulin	16
" γ- "	17
L.E. cells present	10

Pathological Similarities Between Sjögren's Syndrome and Systemic Lupus Erythematosus

Most students of Sjögren's syndrome have assumed that the corneal and conjunctival changes are due only to the reduced secretion of tears; hence the name keratitis sicca. There is, however, a good deal of evidence against this view. Firstly, as Sjögren has pointed out, the eye does not look dry, and with the slit-lamp the globe is seen to be covered with a fluid layer. Secondly, staining of the cornea and conjunctiva in the characteristic fashion with rose Bengal is not well correlated with lack of tears as shown by Schirmer's test; many elderly people have a deficiency of tears yet have no other signs or symptoms of Sjögren's syndrome; on the other hand, some patients who present symptoms of the disease and whose eyes stain in a typical manner with rose Bengal possess almost a normal tear supply (Henderson, 1950). Thirdly, the pathology of Sjögren's syndrome is very different from that which occurs in conditions such as lagophthalmos, in which there is dryness of the eyes. In these conditions keratinization is the characteristic pathological process as in any other mucous surface subject to drying. Keratinization occurs only in very severe Sjögren's syndrome, and then to a slight degree; in these cases the bulb does tend to lose its natural sheen.

It is unjustifiable, therefore, to regard the ocular changes as being brought about solely by desiccation of the epithelium. This was pointed out by Sjögren. He thought the changes in the eye could be explained as compensatory attempts by the conjunctiva to secrete fluid to make up for the lack of tears. The changes in the goblet cells in the lower fornix could be explained in this way, but not the other changes in the cornea and conjunctiva.

A review of the histology of Sjögren's syndrome shows how well it accords with that of systemic lupus. Oedema, early destruction of elastic tissue, hyalinization, infiltration with lymphocytes and plasma cells, fibroblastic proliferation, and thickening of blood-vessel walls with hyaline tissue all occur in systemic L.E. The

TABLE II.—*Clinical and Pathological Features of 28 Patients with Sjögren's Syndrome*

Case No.	Age and Sex	Duration of Ocular Symptoms in Years	Joints	Skin	Hb (g.%)	E.S.R. Wintrobe mm./1 hr.	W.B.C. (c.mm.)	Platelets (c.mm.)	Serum Protein (g.%)	Albumin (%)	α_2 Globulin (%)	γ Globulin (%)	L.E. Cells	Remarks
1	57 F	2	Arthralgia	Purpura. Koilonychia	15·5	15	5,000	180,000	6·5	44	13	21	None	(L) Horner's syndrome. No cause found
2	66 F	3	,,	Chilblains	15·9	11	7,300	205,000	7·6	49	8	24	,,	
3	43 F	5	Rheum. arthritis	Erythematous rash on face	11·7	19	8,000	113,000	7·6	53	10	19	,,	Iron-deficiency anaemia. Thyroidectomy, 1953. No histological report
4	59 F	3	,,	Chilblains	11·5	44	5,700	320,000	7·3	45	13	23	Numerous	Coombs test negative. Perforated corneal ulcer. Cytoid body in retina
5	53 F	10	Arthralgia	Rosacea facies	13·5	9	6,700	350,000	7·0	54	12	17	None	
6	51 F	4	,,	Chilblains. Psoriasis	13·5	20	8,000	290,000	6·8	60	10	13	,,	
7	66 F	6	Rheum. arthritis	Normal	13·3	49	1,200	173,000	7·7	48	8	27	,,	Recurrent bilateral uveitis 4 years. No cause found. *X*-ray chest: hilar adenopathy, fine nodularity through all zones of both lungs — appearance compatible with lupus lung.
8	59 F	2	,,	Raynaud's phenomenon. Psoriasis	15·5	15	4,400	340,000	7·5	60	5	15	,,	Bilateral uveitis 4 yrs. No cause other than toxoplasmosis. Dye test 1/32; complement-fixation test positive 1/4
9	63 F	2	,,	Chilblains	14·1	15	3,600	210,000	7·0	59	10	12	,,	Recurrent iritis. No cause found
10	68 F	18	Normal	Purpura	17·8	3	8,400	195,000	7·8	57	8	16	,,	
11	53 F	3	Rheum. arthritis	Photosensitivity	13 0	48	7,300	420,000	7·2	56	9	17	,,	Is on delta-steroid and corticotrophin for arthritis
12	72 F	8	,,	Normal	13·5	17	5,000	200,000	7·0	Normal	Normal	Normal	,,	
13	74 F	11	Arthralgia	Raynaud's phenomenon. Purpura	13·6	37	5,700	169,000	7·2	48	10	14	Very few	β-globulin raised to 23%. Recurrent parotid enlargement for 10 years
14	75 F	4	Rheum. arthritis	Normal	13·6	40	2,300	110,000	7·8	51	6	28	None	Enlarged liver and spleen. Liver-function tests normal apart from proteins. Felty's syndrome. Goitre removed 1945. No histological report
15	54 F	3	,,	Purpura. Photosensitivity	16·5	5	8,000	200,000	5·4	54	10	14	,,	β-globulin raised to 18%
16	69 F	6	,,	Normal	14·4	40	5,700	320,000	7·6	40	14	23	1 found	,, ,,
17	48 F	5	,,	Dermatitis following gold injections	12·6	41	4,100	340,000	6·8	43	10	29	None	
18	47 F	7	,,	Raynaud's phenomenon. Photosensitivity	10·8	35	3,400	220,000	7·8	36	11	34	Moderate numbers	Iron-deficiency anaemia. Mitral stenosis—no history of rheumatic fever
19	60 F	13	Arthralgia	Raynaud's phenomenon	14·4	30	5,000	250,000	7·2	43	9	29	Small numbers	Coombs text negative. Petit mal since childhood and Jacksonian epilepsy 5 years. Arteriogram and air encephalogram normal. Recurrent colitis. Parotid swellings 3 years
20	35 F	7	Rheum. arthritis	Chilblains. Raynaud's phenomenon. Urticaria. Photosensitivity	13·9	22	8,000	230,000	8·3	32	13	34	Large numbers	Coombs test negative. Bronchospasm and attack of collapse (R) lower zone, final *X*-ray chest N.A.D. Episcleritis; perforated corneal ulcer
21	53 F	2	,,	Normal	Not done	Not done	Not done	Not done	8·6	46	13	23	Small numbers	(R) homonymous hemianopia 2 yrs. No cause found. B.P. 130/90. Recurrent colitis
22	60 F	3	Normal	Chilblains. Purpura	14·7	19	7,300	170,000	8·2	31	14	39	None	
23	60 F	3	Rheum. arthritis	Purpura	15·2	22	8,900	240,000	7·4	42	13	24	Small numbers	β-globulin raised to 16%. Severe mental depression. Goitre removed 1927 — no histological report
24	67 F	1	,,	Normal	11·4	Not done	2,700	Not done	6·8	43	6	36	Small numbers	Enlarged spleen. Bone marrow hypocellular. Felty's syndrome. Hypopyon ulcer, 1957
25	50 F	10	Arthralgia	Purpura. Chilblains	14·5	4	4,000	200,000	7·6	53	9	18	None	β-globulin raised to 15%. Diffuse enlargement of thyroid, no toxic signs
26	70 F	3	,,	Raynaud's phenomenon. Chilblains	14·8	26	4,700	190,000	7·6	54	7	24	,,	Albuminuria
27	62 F	10	Rheum. arthritis	Leg ulcers. No varicose veins	12·6	36	4,700	410,000	7·7	48	7	25	,,	
28	83 F	13	Arthralgia	Normal	9·8	31	4,100	380,000	7·4	52	10	23	Numerous	Iron-deficiency anaemia. Recurrent pleurisy

oval bodies found by Sjögren in the substantia propria of the cornea and in the sclera which stain blue with haematoxylin may well be haematoxyphil bodies. These were described by Klemperer *et al.* (1950) as being pathognomonic of systemic lupus and as originating in an alteration of the nuclei of mesenchymal cells. They are about the size of a lymphocyte or larger, stain purple blue with haematoxylin, and are chiefly ovoid or spindle-shaped. Cytochemical methods have shown that the bodies contain partially depolymerized desoxyribose-nucleic acid. Unfortunately an opportunity has not yet arisen in which these methods could be applied to the bodies that occur in Sjögren's syndrome.

The bulbar changes of Sjögren's syndrome occur in that part of the bulb which is most exposed to light and the slight mechanical trauma of blinking. Sensitivity to light is a prominent feature of systemic lupus; and the skin lesions tend to develop in areas subject to friction or mechanical trauma. It may be that sunlight and/or mechanical trauma are precipitating factors in the development of the corneal and conjunctival changes of Sjögren's syndrome.

Necropsies on nine patients with Sjögren's syndrome have been fully reported in the literature (Bruce, 1941; Reader *et al.*, 1951; Ellman *et al.*, 1951; Haas, 1951; Morgan and Raven, 1952; Morgan, 1954; Cardell and Gurling, 1954). In only one (Morgan, 1954) was systemic L.E. diagnosed. However, the diagnosis of systemic L.E. at necropsy is notoriously difficult. Many of the findings in these necropsies are very suggestive of systemic lupus. For example, pericarditis was found in four, pleurisy in three, interstitial pneumonitis in two, enlarged lymph nodes in five, splenomegaly and perisplenitis in two, hepatomegaly and changes similar to those of lupoid hepatitis in two, and arteritis in three. Most of these patients died rather mysterious deaths, and this is typical of patients dying with systemic L.E.

Clinical and Clinico-pathological Similarities Between Sjögren's Syndrome and Systemic L.E.

Tables III and IV list the clinical and clinico-pathological features common to Sjögren's syndrome and systemic L.E. The frequency of the various manifestations of systemic lupus and even more those of Sjögren's syndrome varies considerably from author to author. Some quite common features of systemic lupus (such as pericarditis and a false-positive W.R.) have rarely been looked for in Sjögren's syndrome, thus precluding an accurate estimate of their frequency.

It is of interest to note that Shearn and Pirofsky (1952) found photophobia in 18% of their cases of systemic lupus and "optic abnormalities" other than funduscopic ones in 47%. It is possible that some of these patients had Sjögren's syndrome.

L.E. Cells and Sjögren's Syndrome.—L.E. cells have rarely been found in Sjögren's syndrome (Morgan, 1954; MacLean and Robinson, 1954; McLenachan, 1956), but they have not been looked for before in a series of cases. Probably more would be found if these patients were examined for the presence of L.E. cells at intervals over several years, as it is well known that repeated examinations may be necessary to obtain a positive test. Not all known cases of systemic lupus have a positive L.E. cell test; Wilkinson and Sacker (1957), in reviewing several reported series of systemic lupus, found the average incidence of a positive L.E. cell phenomenon to be 82%. In many large surveys no false-positive tests have been found: but a positive L.E. cell phenomenon has been reported in severe drug reactions, especially to hydrallazine, and in a few cases of cirrhosis of the liver (Wilkinson and Sacker, 1957). In gross leucopenia the L.E. cell phenomenon may be negative owing to the low neutrophil polymorph count, as the test partly depends on the number of these cells present; it may also be negative in patients on steroid therapy (Dubois, 1956) (see Case 11).

Mikulicz's Disease.—Morgan and Castleman (1953) and Morgan (1954) have shown that Mikulicz's disease and Sjögren's syndrome are probably identical in that the pathological changes in the salivary glands in the two conditions are the same and clinically the two diseases are similar. In our series Cases 13 and 19

TABLE III.—*Clinical Features Common to Sjögren's Syndrome and Systemic Lupus*

	Sjögren's Syndrome	Systemic Lupus
Sex	85–95% female	80–90% female
Maximum incidence	40–60 years	30–50 years
Clinical course	Episodic	Episodic
Rheum. arthritis	Very common	Very common
Arthralgia	Common	Common
Raynaud's phenomenon and chilblains	,,	,,
Photosensitivity	Fairly common	Fairly common
Purpura	,, ,,	,, ,,
Alopecia	,, ,, (Weber, 1945; Thompson and Eadie, 1956; McLenachan, 1956)	,, ,,
Chronic leg ulceration	Rare	,, ,,
Enlarged parotids	Fairly common	Rare (Shearn and Pirofsky, 1952; Harvey *et al.*, 1954; Morgan, 1954)
Enlarged lymph nodes	,, ,, (Beetham, 1935; Reader *et al.*, 1951; Gurling, 1953)	Common
Splenomegaly	Fairly common (Beetham, 1935; Bruce, 1941; Holm, 1949; Cadman and Robertson, 1952; Gurling, 1953; Thompson and Eadie, 1956)	Fairly common
Hepatomegaly	Fairly common (Bruce, 1941; Cadman and Robertson, 1952, Gurling, 1953; McLenachan, 1956; Thompson and Eadie, 1956)	,, ,,
Pancreatitis	Rare (Cardell and Gurling, 1954)	Rare (Reifenstein *et al.*, 1939)
Pleurisy and pulmonary lesions	Fairly common (Reader *et al.*, 1951; Ellman *et al.*, 1951; Cardell and Gurling, 1954; Eadie and Thompson 1955)	Fairly common
Pericarditis and valvular lesions	Fairly common (Reader *et al.*, 1951; Ellman *et al.*, 1951; Cardell and Gurling, 1954)	,, ,,
Central nervous system involvement	Rare (Sheldon, 1939; Ramage and Kinnear, 1956)	Rare
Polyarteritis nodosa	Rare (Cardell and Gurling, 1954; Ramage and Kinnear, 1956)	,, (Lincoln and Ricker, 1954; Hill, 1957)

Note: Estimates of the frequency of the various features of Sjögren's syndrome are compiled from the literature and from my series. References are given only to little-known manifestations of systemic L.E. Extensive reviews of this disease are by Harvey *et al.* (1954) and Hill (1957).

TABLE IV.—*Clinico-pathological Features Common to Sjögren's Syndrome and S.L.E.*

	Sjögren's Syndrome	S.L.E.
Hypochromic anaemia	Common	Common
Leucopenia	Fairly common (Critchley and Meadows, 1933; Cadman and Robertson, 1952; Gurling, 1953; Thompson and Eadie, 1956)	Fairly common
Thrombocytopenia	Fairly common	,, ,,
Raised E.S.R.	Common	Very common
Lowered albumin	,,	Common
α_2-globulin raised	Fairly common	Fairly common
γ- ,, ,,	Common	Common
Thymol turbidity abnormal	,, (McLenachan, 1956)	,,
False positive W.R.	Rare (Coverdale, 1948)	Fairly common
Albuminurea	,, (Sjögren, 1943; Reader *et al.*, 1951)	,, ,,
L.E. cells	Fairly common	Very common

(Table I) had Mikulicz's disease, and L.E. cells were found in both cases. Therefore Mikulicz's disease is probably a form of systemic L.E.

Felty's Syndrome.—Gurling (1953) and Thompson and Eadie (1956) have reported cases of Sjögren's syndrome with Felty's syndrome, and two more are described in our series (Table I, Cases 14 and 24), one of which (Case 24) had L.E. cells present. The whole picture of Felty's syndrome—leucopenia, splenomegaly, and rheumatoid arthritis—fits that of systemic L.E.

Boeck's Sarcoid.—This has been reported in association with Sjögren's syndrome (Gruber, 1956; Ramage and Kinnear, 1956; Jones and Stevenson, 1957). It should be noted, however, that the skin lesions of sarcoid can easily be mistaken for those of chronic L.E. (Grund, 1950), and the radiological appearances of the chest in sarcoid and "lupus pneumonitis" are similar. Some cases of dry eyes may, however, be due to sarcoidosis, such as the case reported by Jones and Stevenson (1957), but these are more accurately named keratoconjunctivitis sicca and are probably rather rare. It is possible that sarcoidosis and systemic lupus are related (*British Medical Journal*, 1958); Teilum (1948) brackets the two diseases together as allergic hyperglobulinosis.

Sjögren's Syndrome and Lymphadenoid Goitre

The association of hypothyroidism, lymphadenoid goitre, and raised serum cholesterol with Sjögren's syndrome (Gifford *et al.*, 1943; Gruber, 1956; McLenachan, 1956) is interesting. There are striking similarities between lymphadenoid goitre and Sjögren's syndrome. Both are conditions which mainly affect middle-aged women, and the symptoms tend to fluctuate in intensity and to vary from time to time. The E.S.R. is often raised, the gamma-globulin increased, and flocculation tests (thymol turbidity) are abnormal. Cardell and Gurling (1954) noted the close resemblance between the histology of the salivary and lacrimal glands in Sjögren's syndrome and the thyroid in lymphadenoid goitre and the late stages of myxoedema. Infiltration of the glandular tissues with lymphocytes and plasma cells is found in the two conditions, as are lymphoid follicles, giant cells, atrophy of the glandular tissue, and fibrosis.

If the histological and clinical features of Sjögren's syndrome and lymphadenoid goitre are so similar then they may have aetiological factors in common. Riott *et al.* (1956) found that the serum of patients with lymphadenoid goitre contained an antibody to the patient's own thyroglobulin; and postulated that the destruction of the thyroid results from the progressive interaction of thyroglobulin in the gland with the auto-antibody present in the patient's circulation. A similar process therefore may be occurring in patients with Sjögren's syndrome: auto-antibodies being produced by some substance present in the lacrimal and salivary glands. Such a process might be expected in systemic lupus, in which there are gross disturbances in antibody mechanisms.

Summary and Conclusions

Clinical and pathological evidence is produced showing that Sjögren's syndrome, Mikulicz's disease, and Felty's syndrome are manifestations of systemic lupus erythematosus.

Of 28 patients with Sjögren's syndrome examined, 10 had L.E. cells in the peripheral blood and two of these had Mikulicz's disease and one Felty's syndrome.

Furthermore, it is noted that there are many resemblances between Sjögren's syndrome and lymphadenoid goitre, and it is suggested that they may have aetiological factors in common.

The clinical course of systemic lupus erythematosus may extend over many years, and at times the patient may be in apparent good health. During these periods of remission minor evidence of clinical activity, such as arthralgia, sensitivity to the sun, and chilblains, may be discovered. Most cases of Sjögren's syndrome reported in the literature are in this benign phase. Most published reports on cases of Sjögren's syndrome give only a brief cross-section in space–time of the natural history of the disease. A picture of the whole life-history of a number of cases of the syndrome, including necropsies, would, I feel sure, produce even more evidence that Sjögren's syndrome is a form of systemic L.E.

ADDENDUM.—Since this paper was written B. R. Jones (*Lancet*, 1958, **2**, 773) has demonstrated auto-antibodies in Sjögren's syndrome.

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