SJÖGREN'S SYNDROME

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SINCE Sjögren's original paper (Sjögren, 1933) nearly 30 years ago, considerable literature has accumulated on the syndrome that bears his name. The pathology which Sjögren described has been confirmed and amplified from biopsy material (Gurling, 1953; Ehrlich and Greenberg, 1954; Gurling, Bruce-Pearson and Pond, 1954; Bloch, Bunim, Wohl and Zvaifler, 1960; Bloch, Wohl, Ship and Bunim, 1960; Bunim, 1961) and from autopsy findings (Bruce, 1941; Holm, 1949; Ellman, Weber and Goodier, 1951; Haas, 1951; Reader, Whyte and Elmes, 1951; Morgan and Raven, 1952; Cardell and Gurling, 1954). The clinical features have been described in a series of excellent case reports and papers (Stenstam, 1947; Coverdale, 1948; Ellman and Weber, 1949; Henderson, 1950; Littler, 1951; McLenachan, 1956; Thompson and Eadie, 1956; Stoltze, Hanlon, Pease and Henderson, 1960; Bunim, 1961), and the association of the condition with collagen disorders other than rheumatoid arthritis (Ramage and Kinnear, 1956; Stoltze and others, 1960; Bloch, Bunim and others, 1960; Bloch, Wohl and others, 1960; Bunim, 1961), with Mikulicz's syndrome (Morgan and Castleman, 1953; Morgan, 1954), with sarcoidosis (Ramage and Kinnear, 1956; Gruber, 1956) and with thyroid disease (Stoltze and others, 1960; Bloch, Bunim and others, 1960; Bunim, 1961) has been established. Many papers have recorded the effect of steroid therapy (Bourne, 1952; Cadman and Robertson, 1952; Coste, Offret, Faulong and Uro, 1952; Fernandez-Fernandes and Maranon, 1952; Robert, 1952; Ehrlich and Greenberg, 1954; Gaulhofer, 1954; Gurling and others, 1954; Eadie and Thompson, 1955). More recently attention has been focused on the examination of the serum for rheumatoid factor, thyroid antibodies, and antibodies to lacrymal and salivary gland (Jones, 1958; Bloch, Bunim and others, 1960; Bloch, Wohl and others, 1960; Anderson, Gray, Beck and Kinnear, 1961; Bunim, 1961).

This communication describes the clinical and laboratory findings in a group of 30 patients suffering from Sjögren's syndrome who have been observed over a period of a year or more.

Case Material

All except one of the 30 patients were first seen at the Birmingham and Midland Eye Hospital where they had been referred for ophthalmic consultation. They all had kerato-conjunctivitis sicca which diagnosis was suggested by symptoms of itching, burning, smarting, redness, gritty sensation and dryness. The lack of tears was confirmed by Schirmer's test performed before and after nasal stimulation with ammonia. Typical interpalpebral punctate staining of the conjunctiva and cornea with 1% aqueous Rose Bengal was present in all patients and slit-lamp examination of the cornea revealed areas of filamentary keratitis and peripheral vascularized scarring in a few cases. In addition, all but one of the patients had rheumatoid arthritis or xerostomia or both. The diagnosis of rheumatoid arthritis was made on clinical grounds and that of xerostomia largely on the basis of symptoms, though in some cases defective salivary secretion was obvious. No measurements of salivary flow were made.

Sex and Age Incidence

Of the 30 patients, 27 were female and three male. This gross female preponderance accords with the findings of other writers (Holm, 1949; Henderson, 1950; Thompson and Eadie, 1956; Stoltze and others, 1960; Bunim, 1961). The age at onset is shown in Table 1, from which it will be seen that the condition may develop at any adult age.

Clinical Features

The three main disabilities were kerato-conjunctivitis sicca, rheumatoid arthritis and xerostomia. Reference has already been made to the clinical features of kerato-conjunctivitis sicca, but it should perhaps be added that lacrymal gland enlargement was not present in any of the patients. The arthritic symptoms, signs and radiological appearances were exactly the same as those occurring in patients whose sole disability is rheumatoid arthritis and all grades of severity were seen among the 17 so affected.

Xerostomia when severe in degree interfered

TABLE 1

				Age at Onset	
				Range	Mean
Females	..	..	..	17-73	43.3
Males	..	..	..	32-48	39.0
All cases	..	..	..	17-73	42.9

TABLE 2

Main Disabilities	Cases	First Symptom
Kerato-conjunctivitis sicca ..	All	In 13
Xerostomia	23	In 1
Rheumatoid arthritis	17	In 16

FIG. 1.—Age of onset and duration of major symptoms.

with diction and mastication and inspection of the mouth and tongue showed obvious dryness. Except for the presence of salivary gland enlargement in some instances lesser degrees of xerostomia were without objective abnormality and dryness of the mouth was the only relevant symptom.

In 16 of the 17 patients who had rheumatoid arthritis this produced the first symptom (Table 2) preceding all other manifestations by many years in 13 instances (Fig. 1). Kerato-conjunctivitis sicca developed first in 13 of the group (Table 2) and in five of these it had been present for a period of years before other features of the syndrome followed (Fig. 1). In only one of the patients did xerostomia occur before either of the other two main disabilities.

Most of the 30 patients had additional abnormalities. These are listed in Table 3 from which it will be seen that salivary gland enlargement occurred in eight of the patients, the parotid being affected in seven instances and the sub-maxillary gland in one. Usually there were single or repeated episodes of painful unilateral or bilateral swelling lasting two or three weeks. In

recurrent cases bouts of swelling continued for up to ten or more years and in a minority of patients there was some degree of permanent enlargement. All save one of those with salivary gland enlargement had xerostomia. One patient (Case 19) suffered severely from dysphagia for which no cause was apparent on radiological examination. This symptom was presumably attributable to involvement of the oesophagus by the same pathological process that affects the lacrimal and salivary glands, but no attempt was made to obtain histological proof of this in view of the patient's advanced age. Two other patients (Cases 8 and 10) were troubled by bronchitis. Such an incidence of bronchitis is not remarkable, but here again the symptoms may have resulted from involvement of the bronchial mucosa by the Sjögren process. In only one instance was loss of hair a feature (Case 30). Seven of the patients had Raynaud's phenomenon and five had dermatological lesions. In one it was eczematous (Case 26), in two contact dermatitis (Cases 3 and 5) and in the other two dermatitis medicamentosa (Cases 1 and 24). One patient (Case 30) had had purpura and swelling of the legs provoked by

TABLE 3

Other Features	No. of Cases
Salivary gland enlargement (all except one had xerostomia):	
(i) Parotid	7
(ii) Submaxillary	1
Raynaud's phenomenon	7
Leucopænia (below 4,000 per cu. mm.) ..	3
Bronchitis	2
Dysphagia	1
Purpura hyperglobulinæmia	1
Skin lesions:	
(i) Dermatitis medicamentosa	2
(ii) Contact dermatitis	2
(iii) Eczema	1
Iritis	1
Loss of hair	1

TABLE 4
HÆMATOLOGY

(Anæmia when present is usually associated with rheumatoid arthritis or some unrelated condition)

	No. of Cases	With Rheumatoid Arthritis	Other Factors
Hb. %:			
60-69 ..	2	2	Uræmia, 1 case
70-79 ..	7	6	Carcinoma of stomach, 1 case
80-89 ..	9	3	Duodenal ulcer, 1 case
90-99 ..	9	—	—
100-109 ..	2	—	—
110-120 ..	1	—	—
White-cell count:			
Under 2,000	1	0	None found
2,000-3,000	0	—	—
3,000-4,000	2	1	None found
4,000-5,000	7	4	—
5,000-6,000	3	0	—
6,000-7,000	3	3	—
7,000-8,000	4	1	—
8,000-9,000	6	6	—
9,000-10,000	2	0	—
10,000-11,000	2	2	—

standing and disappearing with rest for six years. This was associated with a high level of 7s globulins. Similar cases have been recorded by previous writers (Waldenström, 1952; Kay and Robertson, 1955; Symon, Rohn and Bond, 1957; Strauss, 1959). Three patients (Cases 8, 11 and 14) were leucopænic. This feature is referred to more fully with the other hæmatological findings.

Hæmatological Findings

The hæmatological findings are shown in Table 4 from which it will be seen that only nine of the 30 patients were appreciably anæmic. Of

TABLE 5
SERUM PROTEINS

Precipitation method:		
Albumin	Mean: 4.1 g./100 ml.	
	Range: 2.4-5.3 g./100 ml.	
Globulin	Mean: 3.5 g./100 ml.	
	Range: 1.9-6.2 g./100 ml.	
	Below 3.6 g./100 ml.: 19 cases	
	Above 3.6 g./100 ml.: 11 cases	
Electrophoresis:		
Albumin	Normal	
Globulin: alpha-1 ..	Some raised, others normal	
alpha-2	Some raised, others normal	
beta	Normal	
gamma	All except one raised, five markedly so.	

Serum protein changes were unrelated to the presence or absence of rheumatoid arthritis.

TABLE 6

Sedimentation Rate (Wintrobe mm./hr.)		Mean: 24.3	
Range: 0-48	Cases	Mean: 24.3	Cases
0-10 ..	8	31-40 ..	5
11-20 ..	6	41-50 ..	6
21-30 ..	5		
Cases:			Mean
With rheumatoid arthritis			26.9
Without rheumatoid arthritis			21.0
With serum globulin above 3.6 g./100 ml.			26.7
With serum globulin below 3.6 g./100 ml.			22.9
With very high gamma globulin			26.2
With normal or moderately raised gamma globulin			23.9

these, eight had rheumatoid arthritis and in two patients other factors (uræmia (Case 4) and carcinoma of the stomach (Case 17)) were probably responsible.

Three patients (Cases 8, 11 and 14) had white-cell counts of less than 4,000/cu.mm. The differential count was normal in each instance and no cause for the leucopænia was apparent. There was no other evidence, except rheumatoid arthritis in Case 8, to support a diagnosis of systemic lupus erythematosus and the only other relevant hæmatological finding was that the sternal marrow showed a reduction in the number of mature polymorphonuclear leucocytes in Case 11. Other writers (Yttrhus, 1947; Littler, 1951; Gurling, 1953; Stoltze and others, 1960; Bunim, 1961) have reported an unexplained leucopænia in 10% of cases of Sjögren's syndrome. Cadman and Robertson (1952) indicated that in such patients the white-cell count rises to normal levels with steroid therapy but steroids were not given to any of our three leucopænic patients.

Search for L.E. cells and the L.E. slide test was negative in all cases.

Serum Proteins

The serum proteins were estimated in all patients by the precipitation method and by electrophoresis. The findings are summarized in Table 5. By the precipitation method the mean levels were just within the normal range, but in ten patients the serum albumin was below 4.0 g./100 ml. and in 11 the serum globulin was above 3.6 g./100 ml., in one patient being as high as 6.2 g./100 ml. By the electrophoretic method the serum albumin was normal in all cases, while of the globulin fractions the alpha-1 and alpha-2 were raised in some patients and normal in others, the beta fraction was normal in all and the gamma globulin was raised in all patients except one, being markedly elevated in five. Ultracentrifuge analysis was carried out in one patient only (Case 30) who had orthostatic purpura. This showed high γ s globulins (2.34 g./100 ml.), normal 1 γ s and 4.5 γ s globulins and no 2 γ s or 3 γ s globulins. Where abnormal the serum protein changes were unrelated to the presence or absence of rheumatoid arthritis.

Sedimentation Rate

The sedimentation rate was estimated by the Wintrobe method and was found to be elevated in 16 of the patients (Table 6). In those with rheumatoid arthritis it was a little higher than in those not so affected, while slightly higher levels were present in those with serum globulins above 3.6 g./100 ml., and in those with gross elevation of the gamma fraction than in the remainder.

Radiology

Four of the chest radiographs (Cases 2, 8, 10 and 21) showed old or recent inflammatory lesions at the bases or in the mid-zone (Fig. 2). The remainder showed no relevant abnormality. Involvement of the bronchia mucosa by the Sjögren process is well recognized (Cardell and Gurling, 1954; Ellman and others, 1951; Reader and others, 1951; Bucher and Reid, 1959) and the occurrence of inflammatory lesions in the lower respiratory tract has been reported by numerous writers (Ellman and Weber, 1949; Cardell and Gurling, 1954; Thompson and Eadie, 1956; Stoltze and others, 1960; Bunim, 1961).

Radiography of the salivary glands showed parotid calcification in one patient only (Case 2, Figs. 3 and 4) and unilateral parotid enlargement in another (Case 21). The remainder were normal. Parotid calcification has been previously described by Cardell and Gurling (1954).

Sialography was not done in any of our cases as it was not thought likely to be of any benefit to the patient, and the procedure carries with it a slight risk of producing a suppurative parotitis.

FIG. 2.—Chest radiograph of Case 2 showing inflammatory shadowing at both bases.

Other writers (Cardell and Gurling, 1954; Gurling and others, 1954; Bloch, Wohl and others, 1960; Bunim, 1961) have found sialectasis and a reduced number of branch ducts.

Thyroid Abnormalities

Four of the patients (Cases 9, 19, 22 and 30) had non-toxic goitres and a further two had undergone partial thyroidectomy, one (Case 3) for colloid goitre and another (Case 7) for hyperthyroidism. The latter patient was thought to be still suffering from thyrotoxicosis. The remaining patients showed no clinical evidence of thyroid disease. There was nothing to suggest thyroiditis in any of the group and none was myxoedematous.

There was a family history of thyroid disease in three of the 30 patients (Cases 7, 29 and 30) and one of these three had a toxic (Case 7), another a non-toxic goitre (Case 30).

The tanned red-cell test for thyroglobulin antibodies (Table 7) was positive in 16 and negative in the remaining 14 of the patients, and precipitating antibodies to thyroid were found by the agar gel method in ten patients and a doubtful positive result was obtained in a further two. Complement-fixing antibodies to thyroid were present to normal thyroid in seven patients and to toxic thyroid in these seven and another three (Table 7).

FIGS. 3 and 4.—Parotid radiographs of Case 2 showing stippled calcification on right.

There was no correlation between the finding of antibodies by any of the three methods, and the presence or absence of clinical evidence of thyroid disease. The group of 16 in whom the tanned red-cell test showed thyroglobulin antibodies to be present were unrelated to the groups in which precipitating and complement-fixing antibodies were found. In fact the only tangible links in the mass of data relevant to the thyroid in this group were the facts that all those showing complement-fixing antibodies to normal thyroid also showed complement-fixing antibodies to toxic thyroid and six of the seven showing complement-fixing antibodies to normal thyroid, and eight of the ten showing complement-fixing antibodies to toxic thyroid also showed precipitating antibodies to thyroid by the agar gel technique.

The relationship of thyroid antibodies to the presence or absence of rheumatoid arthritis is of interest in that the 13 patients without rheumatoid arthritis showed a significantly higher incidence of precipitating antibodies ($P = 0.05$ to 0.02) and complement-fixing antibodies ($P = 0.01$ to 0.001) to thyroid than did the 17 patients who had rheumatoid arthritis. The significance is even higher ($P = 0.001$) if both types of antibody are considered together.

Rheumatoid Factor

The latex fixation test was done in all the 30 patients and the Rose-Waaler test in all except one. The results obtained are shown in detail in Table 7 and summarized in Table 8. It will be seen that of the 17 patients with rheumatoid arthritis three had a negative latex fixation test and five a negative Rose-Waaler test. The only apparent relationship to other findings is that all those showing complement-fixing antibodies to thyroid or toxic thyroid had a positive latex fixation test.

Antibodies to Salivary and Lacrymal Glands

An attempt was made to isolate specific antibodies to lacrymal and salivary glands. The sera of 28 of the 30 patients were examined for precipitating antibodies by the agar gel technique and for complement-fixing antibodies. The detailed results are shown in Table 9 from which it will be seen that precipitating antibodies to salivary gland were found in 12 patients, all of whom had xerostomia, but in all save two doubtfully positive cases precipitating antibodies to thyroid were also present. Complement-fixing antibodies were found to salivary gland in eight patients, all of whom had xerostomia, and to lacrymal gland in

TABLE 7

INCIDENCE OF THYROID DISEASE AND RHEUMATOID ARTHRITIS, OF THYROID ANTIBODIES AND RHEUMATOID FACTOR AND OF FAMILY HISTORY OF THYROID DISEASE AND RHEUMATOID ARTHRITIS IN THE GROUP STUDIED

Case Number	Family History of Thyroid Disease	Goitre or Thyroidectomy	Tanned Red-cell Test for Thyroglobulin Antibodies	Precipitating Antibodies to Thyroid by Agar Gel Method	Complement-fixing Antibodies		Family History of Rheumatoid Arthritis	Rheumatoid Arthritis	Latex Fixation Test	Rose-Waaler Test
					Thyroid	Toxic Thyroid				
1			1/25					+		
2			1/25	+			+		±	
3		+					+			
4			1/25					+	+	1/128
5								+	+	1/256
6			1/2,500					+	+	1/16
7	+	+	1/25			1/8	+		±	
8				±				+	+	1/64
9		+						+	+	1/256
10				+		>1/128		+	+	
11			1/2,500	+	1/64	>1/128	+		±	1/64
12								+	+	
13			1/2,500					+	+	1/16
14					1/8	>1/128			±	
15			1/25				+	+		
16								+	+	1/512
17							+	+	+	1/16
18			1/25,000				+	+	+	
19		+					+		+	1/32
20			1/25,000	+		>1/128			+	
21			1/25	+				+	+	1/256
22		+	1/2,500	+	>1/128	>1/128	+		+	
23			1/25						+	1/64
24				+	>1/128	>1/128			+	1/64
25			1/25							
26							+	+	+	1/512
27				+	>1/128	>1/128	+		±	
28			1/250	±				+		1/16
29	+		1/25	+	>1/128	>1/128	+		+	
30	+	+		+	>1/128	>1/128	+	+	+	
Total	3	6	16	12	7	10	13	17	25	15

TABLE 8

Rheumatoid Factor	No. of Cases	No. with Rheumatoid Arthritis
<i>Latex fixation test:</i>		
(i) Negative	5	3
(ii) Positive	25	14
<i>Rose-Waaler Test:</i>		
(i) Negative	14	5
(ii) Positive: 1 in 16	4	4
1 in 32	1	0
1 in 64	4	1
1 in 128	1	1
1 in 256	3	3
1 in 512	2	2

three patients, each of whom had kerato-conjunctivitis sicca, but in all instances save two antibodies were found in higher titre to other tissues and in these two (Cases 2 and 6) the dilutions were only just significant. The most striking finding was that all patients who showed or gave a history of salivary gland enlargement had precipitating antibodies to salivary gland, four of them had complement-fixing antibodies to salivary gland in high titre (the sera of two others were anticomplementary) and among them were the three who had complement-fixing antibodies to lacrymal gland (Table 10). The results in respect of lacrymal gland might have been more impressive if fresh extracts had been available.

Pathology

None of the 30 patients has died during the period in which they have been under observation, so we have no autopsy histology to present and we have not felt justified in subjecting any of them to biopsy of salivary or lacrymal glands or other tissues in view of the fact that the pathological features of the condition are so well documented in the literature. In the salivary and lacrymal glands there is an infiltration with lymphocytes and plasma cells and an atrophy of the acini together with a proliferation of duct lining cells leading to narrowing of ductal lumen and the formation of solid cell masses or nests termed epi-myoeptithelial islands (Reader and others, 1951; Gurling, 1953; Ehrlich and Greenburg, 1954; Gurling and others, 1954; Bucher and Reid, 1959; Bloch, Wohl and others, 1960; Bunim, 1961). In very advanced cases no acinar tissue remains and all that can be recognized are occasional atrophic ducts and chronic inflammatory cells in a mass of fibrous and adipose tissue. Similar changes to those occurring in the salivary and lacrymal glands are found in the tongue, mouth, pharynx, oesophagus, nose, larynx, trachea and bronchi and in the skin (Ellman and

TABLE 10
ANTIBODIES TO SALIVARY AND LACRYMAL GLANDS IN THOSE WITH PAST OR PRESENT SALIVARY GLAND ENLARGEMENT

Case No.	Precipitating Antibodies to Salivary Gland by Agar Gel Method	Complement-fixing Antibodies	
		To Salivary Gland	To Lacrymal Gland
2	+	—	1/8
11	+	Anti-complementary	1/16
20	+	1/64	—
21	+	Anti-complementary	1/8
22	+	—	—
27	+	> 1/128	—
29	+	1/64	—
30	+	> 1/128	—

others, 1951; Cardell and Gurling, 1954). Arteritis has been reported in eight cases (Haas, 1951; Cardell and Gurling, 1954; Ramage and Kinneer, 1956; Bucher and Reid, 1959), sometimes associated with a peripheral neuropathy (Bunim, 1961).

Course and Prognosis

Although all the components of Sjögren's syndrome are of a progressive nature and no curative treatment is available, one of the features of the 30 patients we have studied is how static their condition appears to have been during the period of observation and how long the history in some still merely inconvenienced rather than disabled by the disease. The arthritis is the main threat to independence, but as has already been stated its behaviour differs in no way from that of uncomplicated rheumatoid arthritis. Arteritis and neuropathy have not been seen in this group but the grave prognostic significance of such developments in rheumatoid arthritis is recognized by all who have seen them. The kerato-conjunctivitis sicca is more a source of discomfort than destructive of vision, but the corneal component not uncommonly leaves opacities sufficiently central to diminish visual acuity, while the occurrence of superimposed infection may lead to loss of the eye. In three of our 30 patients vision was reduced to one-half by corneal lesions and one patient came very near to losing an eye from hypopyon ulceration. The xerostomia when at all serious in degree is a very troublesome symptom but has no serious significance though the recurrent attacks of salivary gland enlargement may produce considerable pain. Involvement of bronchi by the Sjögren process with a resultant tendency to bronchitis and episodes of pneumonia seems to carry with it approximately the same

TABLE 9
TISSUE ANTIBODIES

Case No.	Precipitating Anti- bodies by Agar Gel Method		Complement-fixing Antibodies											
	Thyroid	Salivary Gland	Thyroid	Toxic Thyroid	Salivary Gland	Lacrimal Gland	Liver	Muscle	Heart	Spleen	Adrenal	Kidney	Spinal Cord	Lung
1														
2	+	+				1/8								
3														
5														
6					1/8									
7		±		1/8					1/8	1/8				
8	±													
9					1/8				1/16					
10	+	+		> 1/128	1/16									
11	+	+	1/64	> 1/128		1/16	> 1/128	1/8		1/8	1/64	1/64	1/64	1/8
12														
13														
14			1/8	> 1/128			1/64		1/64			1/32		
15														
16														
17														
19														
20	+	+		> 1/128	1/64									
21	+	+												
22	+	+	> 1/128	> 1/128			1/8			1/8		> 1/128		
23		±												
24	+	+	> 1/128	> 1/128	> 1/128	1/8	> 1/128	> 1/128	> 1/128	1/64	> 1/128	> 1/128	> 1/128	
25														
26														
27	+	+	> 1/128	> 1/128	> 1/128		> 1/128		> 1/128	> 1/128	> 1/128	> 1/128	> 1/128	
28	±													
29	+	+	> 1/128	> 1/128	1/64		> 1/128				> 1/128	> 1/128		> 1/128
30	+	+	> 1/128	> 1/128	> 1/128		> 1/128					> 1/128	> 1/128	
Total	12	12	7	10	8	3	7	2	5	5	4	7	4	2

threat to working capacity and life expectancy as does chronic bronchitis occurring alone. Similarly the Raynaud manifestations and the dermatological lesions have no greater or less significance than they have under ordinary circumstances.

Treatment

We have found 1% methyl cellulose drops the most helpful measure for mild and moderate degrees of kerato-conjunctivitis sicca and consider them better than artificial tears. Cortisone drops have been used with benefit by other writers (Bourne, 1952; Coste and others, 1952; Gaulhofer, 1954; Thompson and Eadie, 1956), but we have avoided them in our patients because they may facilitate the development of superimposed infection and endanger the eye. More severe cases we have treated by electro-coagulative closure of the canaliculi. This has proved a most satisfactory procedure and has afforded marked relief of ocular symptoms (Figs. 5 and 6). Its value has been pointed out by earlier writers (Henderson, 1950; Sjögren, 1951; Salvi, 1954; Weiner, 1952; Thompson and Eadie, 1956). The sealed punctum may recanalize after a time and the procedure have to be repeated unless the whole of the lacrymal canaliculus is closed.

For the xerostomia a special lozenge consisting largely of glycerin and gelatin has proved helpful. The detailed prescription is given at Appendix B.

Ellman and Weber (1949), Bourne (1952) and Jones (1958) mentioned the use of deep X-ray therapy in the treatment of salivary gland swelling and one of our patients (Case 27) was so treated before she was seen by us. While radiotherapy may reduce the degree of enlargement its use seems most irrational as it would tend to further diminish the already reduced number of functioning acini and so increase the degree of xerostomia.

The 17 patients who had rheumatoid arthritis were treated as far as their arthritis was concerned in the usual way with physiotherapy, aspirin and its analogues and butazolidin. Some had been given gold injections in the past. In three patients systemic steroid therapy was thought to be indicated because of the very severe widespread active and disabling nature of the rheumatoid process (Cases 4, 9 and 26). In each instance the response of the joints was good but no improvement in the kerato-conjunctivitis sicca or the xerostomia followed. This accords with the experience of other writers (Cadman and Robertson, 1952; Coste and others, 1952; Gaulhofer, 1954; Gurling and others, 1954), some of whom have, however, reported diminution in salivary gland enlargement. The tendency to purpura and swelling of the legs on standing in Case 30 was controlled to some

extent by elastic stockings. The leucopenia found in Cases 8, 11 and 14 was causing no symptoms or disability and was left untreated.

Discussion

Some authorities question whether Sjögren's syndrome is a separate disease entity and whether the diagnostic label is worthy of retention. Certainly the condition does show a good deal of overlap with other diseases and it appears probable that it can develop as an end-result of several different pathological processes. From the clinical point of view, however, there is ample justification for its continued use and if it were discarded it would be difficult to find another diagnostic niche for many of the patients currently so diagnosed.

The work of Morgan (Morgan and Castleman, 1953; Morgan, 1954) has shown that Mikulicz's syndrome has the same histology and symptomatology as Sjögren's and the former term should probably be in the discard.

Among the proven causes of Sjögren's syndrome sarcoidosis appears to have been the basic pathological process in some cases (Gruber, 1956; Ramage and Kinnear, 1956; Crick, Hoyle and Smellie, 1961). Evidence of sarcoidosis was searched for diligently in our 30 cases but none was found and usually Sjögren's syndrome seems to have other origins. Thus a large proportion are associated with collagen disturbances, usually rheumatoid arthritis but sometimes systemic lupus erythematosus, scleroderma or polyarteritis nodosa (Ramage and Kinnear, 1956; Stoltze and others, 1960; Bloch, Bunim and others, 1960; Bloch, Wohl and others, 1960; Bunim, 1961) and in those who show no clinical evidence of collagen disorder there is often rheumatoid factor in the serum or a family history of rheumatoid arthritis. Seventeen of our 30 patients had rheumatoid arthritis and of the remaining 13 all but one had either rheumatoid factor in the serum or a family history of rheumatoid arthritis. It seems therefore not unreasonable to regard Sjögren's syndrome as one of the many variants of collagen disturbance that may affect humans. But on the other hand the frequent association of Sjögren's syndrome with thyroid disease, including Hashimoto's thyroiditis, and the finding of tissue antibodies in their serum make it likely to be an auto-immune disease. All except five of our 30 patients had clinical evidence of thyroid disease or thyroid or thyroglobulin antibodies in their serum.

We have, however, failed to find convincing evidence of antibodies specific to lacrymal and salivary glands such as were reported by Jones (1958), and the presence of antibodies to a wide range of tissue such as our patients have shown

FIG. 5.—Eye before occlusion of lacrimal canaliculus.

FIG. 6.—Eye after occlusion of lacrimal canaliculus.

(Table 9) is a feature of collagen disorders and protein disturbances. Until antibodies specific to lacrimal and salivary glands can be demonstrated auto-immunity cannot be regarded as a proven cause. However, the relatively poor response of Sjögren's syndrome to steroid therapy is out of keeping with the general pattern of collagen and auto-immune diseases and there may well be other unsuspected factors participating in its causation.

Summary

(1) The clinical features of 30 cases of Sjögren's syndrome are presented together with the hæmatological, biochemical and radiological findings.

(2) All except one of the group had either rheumatoid arthritis, the rheumatoid factor in the serum or a family history of rheumatoid arthritis and all except five had clinical evidence of thyroid

disease or thyroid or thyroglobulin antibodies in the blood.

(3) Precipitating antibodies to salivary gland were found in 12 patients and complement-fixing antibodies were found to salivary gland in eight and to lacrimal gland in three. However, in all patients in whom such antibodies were present at a significant level antibodies to other tissues were also found.

(4) Those showing antibodies to salivary and lacrimal glands were closely related to those with past or present salivary gland enlargement.

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APPENDIX A

Case Protocols

Case 1.—Male, aged 50. Developed rheumatoid arthritis affecting hands, wrists and knees at age of 48 and kerato-conjunctivitis sicca a year later. Mouth unaffected but had Raynaud's phenomenon and dermatitis medicamentosa (sulphacetamide). Latex fixation and Rose-Waaler tests negative. Blood count, ESR and serum proteins normal.

Case 2.—Female, aged 60. Twenty years' history kerato-conjunctivitis sicca, and xerostomia since age of 45. No sign of arthritis but had rheumatic fever when 26 and again when 30 and father and two sisters have rheumatoid arthritis. Rose-Waaler negative. Latex fixation test weakly positive. History of cough and repeated respiratory tract infections for some years

and chest radiograph showed inflammatory shadowing both bases (Fig. 2). Parotid radiographs showed stippled calcification on right (Figs. 3 and 4). Blood count and ESR normal. No clinical evidence of thyroid abnormality. Precipitating antibodies to salivary gland and thyroid and complement-fixing antibodies to lacrimal gland (1 in 8) present in serum. Ocular symptoms and signs severe. Excellent response to canaliculi occlusion.

Case 3.—Female, aged 50. Partial thyroidectomy for colloid goitre when 15. Recent onset kerato-conjunctivitis sicca. Also had chrome dermatitis. Father and sister had rheumatoid arthritis but patient showed no joint abnormality and salivation was normal. All investigations negative, including tests for rheumatoid factor.

Case 4.—Female, aged 56. Nephrectomy for pyonephrosis many years ago. Eight-year history of rheumatoid arthritis affecting hands, wrists, elbows, shoulders, feet, ankles and knees. Olecranon nodes and enlarged axillary glands present. Kerato-conjunctivitis sicca for 18 months and xerostomia for a year. Urine contained albumin and pus and blood urea 150 to 250 mg./100 ml. Hb. 65%. Auricular fibrillation and cardiac failure. Chest radiograph showed gross cardiac enlargement but no other abnormality. Electrocardiograph normal apart from auricular fibrillation. Latex fixation test positive and Rose-Waaler positive at 1 in 128. Arthritis responded well to dexamethasone but no improvement in eyes or mouth resulted. Cardiac and renal function improved with rest, digoxin and antibiotics.

Case 5.—Female, aged 59. Twenty-year history of rheumatoid arthritis affecting chiefly hands, knees and ankles. Worse last three years. Treated with butazolidin and aspirin. Kerato-conjunctivitis sicca for five years. Recurrent corneal ulceration. Right eye worse than left. Good response to canaliculi occlusion. Mouth and nose dry three years. Metal varnish contact dermatitis. Chest radiograph normal apart from old Ghon lesion. Hb. 74%, ESR 29 mm./hr. Latex fixation test positive. Rose-Waaler positive at 1 in 256.

Case 6.—Female, aged 72. Severe, widespread and grossly disabling rheumatoid arthritis for 36 years. Kerato-conjunctivitis sicca for 30 years and xerostomia for three years. Three-year history of diarrhoea and tender mass palpable left side of pelvis. Barium enema confirmed the presence of severe diverticulitis. Hb. 72%, ESR 48 mm./hr. Latex fixation test positive and Rose-Waaler positive at 1 in 16. Complement-fixing antibodies to salivary gland in a dilution of 1 in 8. No clinical evidence of thyroid disease but thyroglobulin antibodies present at 1 in 2,500. Ocular condition improved following occlusion of canaliculi but localized scleromalacia becoming apparent.

Case 7.—Female, aged 44. Partial thyroidectomy for thyrotoxicosis when 38. BMR still +36% and PBI 11.2 µg./100 ml. Mild asthma for some years. During past year developed first kerato-conjunctivitis sicca and then xerostomia. No evidence of rheumatoid arthritis but mother suffered from it and two relatives have thyroid disease. Latex fixation test weakly positive. Thyroglobulin antibodies present at 1 in 25 and complement-fixing antibodies to toxic thyroid at 1 in 8.

Case 8.—Female, aged 73. Rheumatoid arthritis affecting chiefly hands for 48 years. Kerato-conjunctivitis sicca since 51 and xerostomia since 53. Mouth bone dry on inspection. Troubled by bronchitis for some years. Chest radiograph showed calcification in both mid-zones and fibrosis and old pleurisy at the right base. Hb. 76%, w.b.c. 3,700/cu.mm., normal differential. Serum proteins normal and no L.E. cells. Urine normal. ESR 47 mm./hr. Latex fixation test positive and Rose-Waaler positive at 1 in 64.

Case 9.—Female, aged 58. Rheumatoid arthritis affecting chiefly hands, wrists, elbows, shoulders and ankles for 22 years. Much disability. Kerato-conjunctivitis sicca for nine years and recent onset of xerostomia. Non-toxic goitre. Blood count normal. ESR 28 mm./hr. Latex fixation test positive and Rose-Waaler positive at 1 in 256. No thyroid antibodies but complement-fixing antibodies to salivary gland (1 in 8) and to heart (1 in 16). Treated with prednisone. Arthritis responded well but no improvement in mouth or eyes. Schirmer's test: 1 mm. each eye before and after three months' steroid therapy.

Case 10.—Female, aged 61. Three years' history of rheumatoid arthritis and xerostomia and recent onset of kerato-conjunctivitis sicca. Hypertensive and severe bronchitic tendency. Chest radiograph showed evidence of old pleurisy at both bases. Hb. 80%, ESR 39 mm./hr. Ocular symptoms and signs severe. Good response to canaliculi occlusion.

Case 11.—Female, aged 48. Kerato-conjunctivitis sicca since age 17. Xerostomia for ten years. Enlarged submaxillary salivary gland four years. Also had Raynaud's phenomenon. No evidence arthritis but father and sister have rheumatoid arthritis, latex fixation test weakly positive and Rose-Waaler positive at 1 in 64. Precipitating antibodies to salivary gland and complement-fixing antibodies to lacrimal gland (1 in 16), but also to thyroid, liver, muscle, spleen, adrenal, kidney, spinal cord and lung. Hb. 80%, w.b.c. 1,800/cu. mm., normal differential. Platelets normal. Sternal marrow: reduced number mature polymorphonuclear leucocytes. ESR 41 mm./hr. Serum proteins normal. No L.E. cells. Urine normal. Small nodule excised from leg: histologically a melanoma. No sign of recurrence to date.

Case 12.—Female, aged 53. Rheumatoid arthritis affecting hands, feet and elbows for 21 years. Some nodule formation. Hb. 69%, MCHC 28%, ESR 40 mm./hr. Latex fixation test positive, but Rose-Waaler negative. Recently developed kerato-conjunctivitis sicca and xerostomia.

Case 13.—Female, aged 69. Rheumatoid arthritis involving hands, wrists, shoulders and feet for 15 years. Latex fixation and Rose-Waaler tests positive. Kerato-conjunctivitis sicca since 59 and xerostomia since 61. Also a duodenal ulcer which had been treated with belladonna in the past but not recently. Other investigations showed no relevant abnormalities.

Case 14.—Female, aged 75. Kerato-conjunctivitis sicca for two years and xerostomia for a year. Joints normal. No family history of arthritis, Rose-Waaler test negative and latex fixation test only weakly positive. Hb. 88%, w.b.c. 3,900/cu. mm., normal differential and no other haematological abnormality. Serum proteins normal and no L.E. cells. Urine normal. Serum showed complement-fixing antibodies to thyroid, liver, heart and kidney. Kerato-conjunctivitis sicca severe. Improved with occlusion of canaliculi.

Case 15.—Female, aged 48. Mother and six sisters rheumatoid arthritis. Eleven years' progressive arthritis hands and feet but latex fixation and Rose-Waaler tests negative. Recent onset of kerato-conjunctivitis sicca. Investigations showed no relevant abnormality.

Case 16.—Male, aged 43. Eleven years' history rheumatoid arthritis involving hands, wrists, elbows, shoulders and knees. Latex fixation test positive and Rose-Waaler positive at 1 in 512. Treated in past with steroids which produced symptoms of peptic ulceration. Recent onset of kerato-conjunctivitis sicca. No xerostomia but nodularity of parotids evident.

Case 17.—Female, aged 67. Two sisters have rheumatoid arthritis, which patient also developed at age of 37. Nearly all joints involved and considerable dis-

ability. Latex fixation test positive and Rose-Waaler positive at 1 in 16. Developed kerato-conjunctivitis sicca at age of 66. Salivation normal. Developed progressive anaemia and abdominal pain. Mass became palpable which at laparotomy was found to be an inoperable gastric carcinoma.

Case 18.—Female, aged 66. Sixteen years' history of rheumatoid arthritis. Recent onset of kerato-conjunctivitis sicca. Salivation normal. Hb. 72%, ESR 43 mm./hr. Latex fixation test positive. No clinical evidence of thyroid disease but tanned red-cell test showed thyroglobulin antibodies in a titre of 1 in 25,000. No other antibodies found.

Case 19.—Female, aged 79. Developed kerato-conjunctivitis sicca when 56 and xerostomia and dysphagia when 67. Barium swallow showed no abnormality. Also troubled by Raynaud's phenomenon. No joint abnormality but one sibling has rheumatoid arthritis and latex fixation test and Rose-Waaler test (1 in 32) both positive. Hb. 72%. Non-toxic thyroid adenoma present but no thyroid or other antibodies in serum.

Case 20.—Female, aged 38. Bilateral parotid swellings when 29 and kerato-conjunctivitis sicca since 32. Xerostomia developed a year ago. Also troubled by Raynaud's phenomenon. No joint abnormality and no family history of rheumatoid arthritis but latex fixation test positive. No clinical evidence of thyroid disease but tanned red-cell test showed thyroglobulin antibodies in a dilution of 1 in 25,000 and precipitating antibodies and complement-fixing antibodies (1 in 64) to salivary gland present in serum. Antibodies to thyroid and toxic thyroid also present.

Case 21.—Female, aged 59. Recurrent parotid swellings, xerostomia and kerato-conjunctivitis sicca since 51. Rheumatoid arthritis involving hands, wrists, feet and ankles for three years. Latex fixation test and Rose-Waaler test (1 in 256) positive. Precipitating antibodies to salivary and thyroid glands and thyroglobulin antibodies (1 in 25) present in the serum. Chest radiograph showed fibrotic changes in right mid-zone and parotid radiographs showed enlargement of the left gland but no calcification. Serum globulin 4.8 g./100 ml. and thymol turbidity 8 units.

Case 22.—Female, aged 61. Kerato-conjunctivitis sicca since 25 and xerostomia for six years. History of parotid swellings. Also has peptic ulceration, a non-toxic goitre and Raynaud's phenomenon. Family history of rheumatoid arthritis and latex fixation test positive but no joint abnormality present. ESR 40 mm./hr., serum globulin 4.4 g./100 ml. and thymol turbidity 13.2 units. Thyroglobulin antibodies (1 in 2,500), precipitating antibodies to thyroid and salivary glands and complement-fixing antibodies to thyroid, toxic thyroid, liver, spleen and kidney present in the serum. Developed hypopyon ulceration of right cornea which healed satisfactorily with antibiotics.

Case 23.—Female, aged 61. Kerato-conjunctivitis sicca for ten years and xerostomia since age 53. No family history of arthritis. Tuberculous left shoulder. Other joints normal. Latex fixation and Rose-Waaler tests positive. Chest radiograph normal but shows calcified cervical glands. Thyroglobulin antibodies (1 in 25) and weak precipitating antibodies to salivary gland in the serum.

Case 24.—Female, aged 54. Kerato-conjunctivitis sicca for nine years and xerostomia for eight. History of iritis when age 44. Also had dermatitis medicamentosa (atropine, hyoscine and tetracycline). No family history of arthritis and no objective joint abnormality but ESR

34 mm./hr. and latex fixation test and Rose-Waaler test (1 in 64) positive. Precipitating antibodies to salivary gland (and to thyroid) and complement-fixing antibodies to salivary and lacrimal glands (and also to all other tissues) in the serum.

Case 25.—Female, aged 63. Xerostomia for eight years and kerato-conjunctivitis sicca for six. No other abnormalities and all investigations negative.

Case 26.—Male, aged 48. Mother suffered rheumatoid arthritis. Arthritis left wrist and ankle 11 years. Recurrent hydrarthrosis right knee. Enlarged lymph nodes axillary and inguinal regions. Given gold, 1954. Albuminuria and epidermophytosis of feet followed. Prednisone since 1956. Two years eczema hands and forearms. Latex fixation test and Rose-Waaler test (1 in 512) positive. Kerato-conjunctivitis five years. Salivation normal.

Case 27.—Female, aged 63. Kerato-conjunctivitis sicca and xerostomia for 20 years. Parotid swellings at onset treated by deep X-ray therapy. Mother had rheumatoid arthritis and latex fixation test weakly positive but no objective joint abnormality. Precipitating and complement-fixing antibodies to salivary gland in serum but also to thyroid and almost all other tissues. No clinical thyroid abnormality.

Case 28.—Female, aged 60. Past history of anaemia and Raynaud's phenomenon. Rheumatoid arthritis affecting hands, cervical spine and hip commenced three years ago. Kerato-conjunctivitis sicca and xerostomia have developed since. Hb. 78%. Latex fixation test negative, Rose-Waaler test weakly positive (1 in 16).

Case 29.—Female, aged 47. Twenty years' history of kerato-conjunctivitis sicca. Xerostomia since age 30 and recurrent parotid swellings from age 30 to 44. No joint abnormality but mother had rheumatoid arthritis and latex fixation test positive. ESR 42 mm./hr., serum globulin 4.9 g./100 ml. and thymol turbidity 9 units. No clinical thyroid abnormality. Serum showed antibodies to salivary gland but also to thyroid and other tissues.

Case 30.—Female, aged 54. Arthritis of shoulders and cervical spine since age of 25. Non-toxic thyroid adenoma present since adolescence. Dry mouth with soreness and lack of taste 11 years and dry eyes eight years. Five years ago parotid swellings. Raynaud's phenomenon and very scanty head hair throughout adult life. Six years purpura and swelling of legs provoked by standing and relieved by rest. Never purpura elsewhere. Hb. 84%, w.b.c. 6,000/cu. mm., normal differential, platelets normal; bleeding, clotting and prothrombin times normal. Serum albumin 2.4, serum globulin 6.2, gamma globulin 3.1 g./100 ml., thymol turbidity 18.9 units.

Ultracentrifuge analysis (Dr. Stanworth) showed 2.34 g./100 ml. 7s globulins, normal 19s and 4.5s globulins and no 29s or 38s globulins. Serum contained antibodies to salivary gland but also to thyroid and other tissues.

APPENDIX B

Demulcent Lozenges

Gelatin	20 g.
Glycerin	40 g.
Sucrose	5 g.
Citric acid	2 g.
Sodium Benzoate	0.2 g.
Lemon essence (Rayner 160) ..	0.6 ml.
Amaranth 1%	1.0 ml.
Water	To 100 g.

The above is sufficient for 30 lozenges.

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