Rheum

Southwestern Medical School

Medical Grand Rounds

May 19, 1977

SJÖGREN'S SYNDROME

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I N D E X

I. HISTORICAL ASPECTS

In 1882 Leber (1) described three cases of a filamentary keratitis in which strand or filaments were found implanted on the corneal surface at one end and were hanging free at the other. Later on, this entity was recognized as the principal ocular manifestation of Sjögren's syndrome (SS). In 1888, Hadden (2) reported a case of an elderly woman with dry mouth and dry eyes and introduced the term "xerostomia". That lacrimal gland deficiency was responsible for diminished tearing was not appreciated until 1919 by Fuchs (3) who also recorded the association of parotid enlargement and decreased salivary secretion in the same patient. Gougerot, in France, was mainly responsible for a conceptual expansion of the Sicca complex when he clearly recognized the dryness of the eyes was but one manifestation of a more general condition in which dryness of the mouth, nose, and vulva occurred (4). The association of arthritis and filamentary keratitis was first brought to light by Houwer in 1927 (5) but it was Henrik Sjögren, a Swedish ophthalmologist who after three years of research published a most comprehensive report describing a group of 13 women with filamentary keratitis, which he renamed keratoconjunctivitis sicca, and arthritis (6). He subsequently expanded his studies in a series of communications spanning 20 years. Because of the fact that he recognized the multisystemic involvement in this disease, he concluded that this generalized disorder constituted a nosological entity. Since 1939, the eponym "Sjögren's" syndrome has been

applied to the triad of keratoconjunctivitis sicca (KCS), xerostomia, and rheumatoid arthritis or other connective tissue disease. (Table I). Two of the three major components are generally considered sufficient for the diagnosis. Specific diseases of the salivary or lacrimal glands such as sarcoidosis or tuberculosis should be excluded.

TABLE I.

MAJOR COMPONENTS OF SJÖGREN'S SYNDROME

KERATOCONJUNCTIVITIS SICCA
XEROSTOMIA
RHEUMATOID ARTHRITIS (OR OTHER CONNECTIVE TISSUE DISEASE)

II. EPIDEMIOLOGY

Incidence. As it occurs with many rare diseases, the frequency with which Sjögren's syndrome is recognized depends on the awareness of the physician who sees the patient initially. In addition, the disorder may cause so little discomfort that medical attention is not sought or the patient may not complain specifically of symptoms directly referring to the eye or mouth. For the above reasons, the incidence of Sjögren's syndrome in patients with ophthalmic disease has been estimated to be as common as 1 in 200 (7) or as rare as 1 in 20000 (8). Screening of populations of patients with eye complains by the use of the Schirmer test (9) or rose bengal staining (10) has been attempted.

The results obtained are of little value in view of the lack of controlled studies and the fact that both the Schirmer test and rose bengal staining are not specific for the presence of keratoconjunctivitis sicca. In a study by Bloch and Bunim (11) designed to determine the prevalence of eye abnormalities in relatives of patients with Sjögren's syndrome, a control population was evaluated with the Schirmer test and a 5 per cent positivity was recorded. Stainability with rose bengal was studied by Holm (10) in 500 non-rheumatic subjects between the ages of 60 and 94 years and positive results were observed in 2.6 per cent of this population.

A better estimate of the incidence of Sjögren's syndrome may be obtained from studies in patients with rheumatic diseases. In two separate studies by Holm (10) and Thompson and Eadie (12) 14.2 and 14.3 per cent respectively of patients with rheumatoid arthritis showed positive tests for keratoconjunctivitis sicca. If one employs a conservative estimate of the incidence of rheumatoid arthritis in the general population as 1.5 per cent, then it turns out that the incidence of keratoconjunctivitis sicca in the general population would be 1 in 525. However, only 50 per cent of patients with KCS have associated rheumatoid arthritis so that the true incidence of KCS in the population should approach 0.4 per cent. This estimation has been confirmed by Seifert and Geiler (13) who studied at autopsy the parotid glands of 900 consecutive unselected subjects and found four with the histologic findings of Sjögren's syndrome, an incidence of 0.44 per cent.

Age. Most studies agree that the age of onset of Sjögren's

syndrome ranges from 40 to 60 years. Bloch et al. (14) found the average age at onset of the first symptom of Sjögren's syndrome was 43.8 years. The age at onset of the syndrome in patients with rheumatoid arthritis and in those with Sjögren's syndrome alone was similar, 49 and 52 years respectively. The distribution of ages at the time of diagnosis of the disease in group of 80 patients reported by Shearn (15) is shown in Figure 1. It is interesting to note that in the rare reported cases of Sjögren's syndrome in childhood (15) systemic lupus erythematosus was the most common associated connective tissue disease.

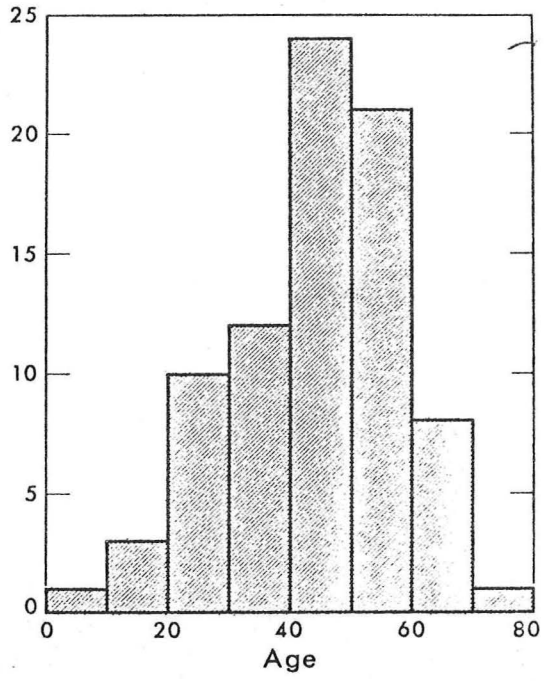

Figure 1. Age at onset of Sjögren's syndrome in 80 patients

Sex. All the studies available have shown a vast preponderance of women over men. Table II shows a list of five studies, in an aggregate of 332 patients the overall incidence in females was 91 per cent.

TABLE II

SEX INCIDENCE IN PATIENTS WITH SJÖGREN'S SYNDROME

AUTHOR	NUMBER OF PATIENTS	PER CENT	REFERENCE
Sjögren	50	96	16
Henderson	104	86	18
Bloch et al.	53	94	14
Mason et al.	45	87	17
Shearn	80	90	15
Total	332	90.6	

The higher incidence in women is interesting when one considers that in uncomplicated rheumatoid arthritis the prevalence of women over men is 3 to 1 whereas in Sjögren's syndrome it is 9 to 1 as shown above. Because of this preponderance, a possible relation to the hormonal make up of the patients has been sought but none has been detected so far.

III. CLINICAL ASPECTS

Initial Manifestations. The disease starts insidiously and it is usually difficult to pinpoint a specific time of inception. The most common initial complaint is arthritis, particularly in groups of patients reported by rheumatologists. In a series of 80 patients (15), 49 had arthritis symptoms.

In 27 patients with arthritis, this symptom preceded the appearance of ocular complaints, in 19, arthritis followed ocular involvement and in 3 both manifestations appeared concurrently. In a large series of 171 patients reported by Whaley et al. (19) 58 per cent presented with arthritis, in the vast majority, the diagnosis of rheumatoid arthritis had been made. In a smaller number of patients, recurrent parotid swelling is the initial presentation. In most series, there is always a small number of patients with SS whose parotid gland has been surgically removed as a result of misdiagnosis.

TABLE III

PRESENTING SYMPTOMS	FREQUENCY %
ARTHRITIS	57
OCULAR SYMPTOMS	24
PAROTID SWELLING	19

Table III shows the frequency of the main modes of presentation in an aggregate population of 313 patients (14,15,19).

Ocular Manifestations. Because of the insidious onset of keratoconjunctivitis sicca, many affected patients do not have any complaints referring to the eyes. In the group with rheumatoid arthritis, the joint pains often constitute the center of attention of the patients so that they may not be aware of the eye symptomatology. Thus, in the group of

patients referred to the NIH (14), presumably with severe involvement, a high proportion had complaints referring to the eyes (Table IV) whereas in a prospective study by Holm (10) 39 per cent of patients with positive rose bengal staining had no ocular symptoms. The same conclusions were drawn by Henderson (18) in a similar study (Table V).

TABLE IV

FREQUENCY OF EYE SYMPTOMS IN 62 PATIENTS

SYMPTOM	PREVALENCE %
FOREIGN BODY SENSATION	74
BURNING	66
EXCESS OF SECRETIONS (ROPY STRANDS)	63
INABILITY TO TEAR IN RESPONSE TO IRRITANTS	63
TIRING, SORENESS, PAIN	57
REDNESS	53
PHOTOSENSITIVITY	53
"FILM"	52
ITCHING	49
CHANGES IN VISUAL ACUITY	32
DIFFICULTY IN MOVING LIDS	23

From Bloch et al (14)

TABLE V

PREVALENCE OF OPHTHALMIC SYMPTOMS IN PATIENT WITH SJÖGREN'S SYNDROME

SYMPTOM	PREVALENCE %
IRRITABILITY OR SORENESS	23
SCRATCHY OR FOREIGN BODY SENSATION	13
BURNING OR SMARTING	16
EXCESS OF SECRETION	11
DRYNESS	9
PHOTOSENSITIVITY	6
ITCHING	5
INABILITY TO LACRIMATE	3
DIMINISHED VISION	1
ULCERS	1

From Henderson (18)

In general, gross examination of the eye is unrewarding. Naked eye examination after conjunctive usually fails to give any indication of dryness. The most common finding is that on non-specific conjunctival injection. Enlargement of the lacrimal glands is quite rare. The most characteristic features on inspection of the eyes is the nature of the ocular secretions which may be thick and tenatious and may form very long strands across the eye.

Only the corneal microscope provides the means to detect

the changes characteristic of this disease. The two features seem most commonly are an increase in precorneal debris and the presence of the epithelial filaments mentioned above. In addition, small pits where the corneal epithelium is denuded can be seen in some patients.

The diagnosis of keratoconjunctivitis sicca is made on the basis of biomicroscopy, performance of the Schirmer test and instillation of rose bengal solution. The Schirmer test is performed by insertion for 5 minutes of a strip of filter paper (Whatman No 41) 5 x 35 mm into the unanesthetized conjuctival sac at the outer or inner third of the lower lid. The paper is folded at a right angle 5 mm from one end prior to insertion and the length moistened is measured starting at the fold. Less than 5 mm wetting is considered abnormal, from 5 to 15 mm the test is inconclusive. As mentioned previously, the Schirmer test is valuable as a screening procedure only, and not as a diagnostic test. The major drawback is due to the large number of false positive results seen a control population. Henderson and Prough (9) found that 33 per cent of patients without eye complaints wetted from 0 to 2 mm., a definite positive result. In general, the values tend to decrease with age, de Roetth (7) found that the average wetting length for octogenarians was 10 to 15 mm with many tests falling in the abnormal range (Table VI).

TABLE VI

AVERAGE SCHIRMER VALUES FOR PRESUMABLY NORMAL PERSONS OLDER THAN FIFTY YEARS

AGE (YEARS)	MEN (mm)	WOMEN (mm)
50-59	32	37.3
60-69	28.3	27
70-79	16.6	18.2
80 and older	10	15

From de Roetth (7)

van Bijstervelt (20) measured tear production by the Schirmer test in 43 patients with SS and in 550 presumably normal persons without eye findings from 20 to 74 years of age. Figure 2 compares the results obtained by van Bijsterveld. The best limit for separating the patient population from the control group was 5.5 mm., using this value, the probability of missing the diagnosis in patients or misdiagnosing a normal was still 15 per cent. For the above reasons, it is clear that the Schirmer test along cannot be used for the definite diagnosis of keratoconjunctivity sicca, there will be a 15 per cent yield of false positive and false negative determinations. Thus, hypolacrimation may be seen in patients other than with Sjögren's syndrome such as in individuals with dehydration

or taking diuretics or drugs affecting the autonomic nervous system.

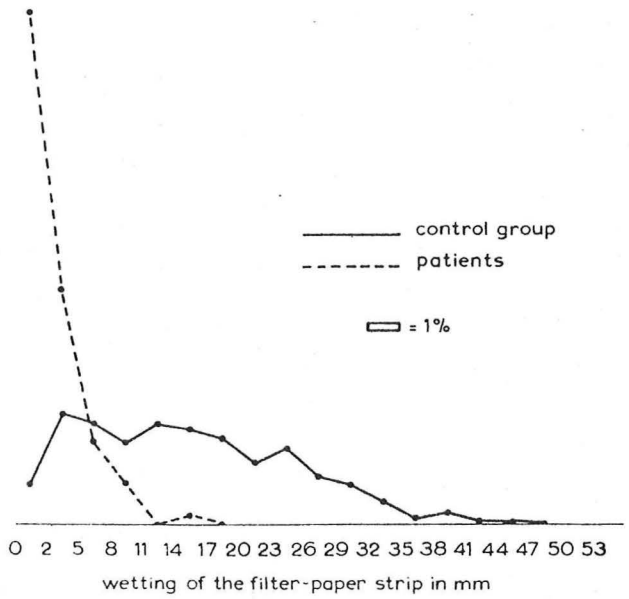

Figure 2- Schirmer test in patients with Sjögren's syndrome compared with normal subjects (20).

Another useful simple test for the detection of keratoconjunctivitis sicca depends on positive corneal staining of devitalized tissue by a 1 per cent solution of rose bengal. Normal eyes may show minimal staining at the edge of the lid, caruncle and plica semilunaris. In patients with fully developed keratoconjunctivitis sicca, brilliant red triangles with their bases towards the limbus fill the palpebral aperture.

The lower two-thirds of the cornea is also stained red.

van Bijsterveld (20) assigned scores up to a maximum of 9 according to the degree of staining of each eye in his study of 43 patients and 550 controls (Figure 3). A staining score of 4 very adequately distinguished between the normal and patient population, the false positive and false negative assignments were only of 4 or 5 per cent respectively. A score of 7 distinguished completely between SS and normal.

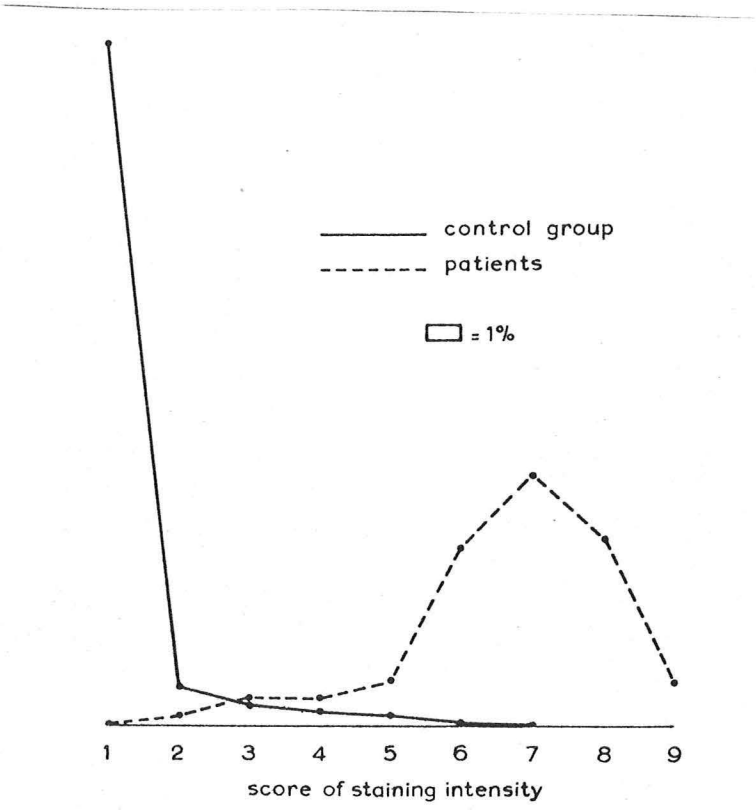

Figure 3. Rose bengal staining in 43 patients with Sjögren's syndrome and 550 normal subjects (20).

This findings suggest that rose bengal staining may be superior to the Schirmer test, indeed, in a study by Holm (10)

six of 18 patients with intense staining had Schirmer values greater than 10 mm. It is also the impression of several ophthalmologists that the intense staining pattern is pathognomonic for Sjögren's syndrome, among 100 patients with chronic conjunctivitis, none showed this type of staining.

In 1948, Meyer (21) suggested that the concentration of lysozyme in tears may be decreased in Sjögren's syndrome. Lysozyme is an enzyme that catalyses the depolymerization of mucopolysaccharides in bacterial cell membranes and represents 30 per cent of the protein content in normal tears (22). Figure 4 shows a normal tear electrophoretic pattern compared to a pattern seen in Sjögren's syndrome.

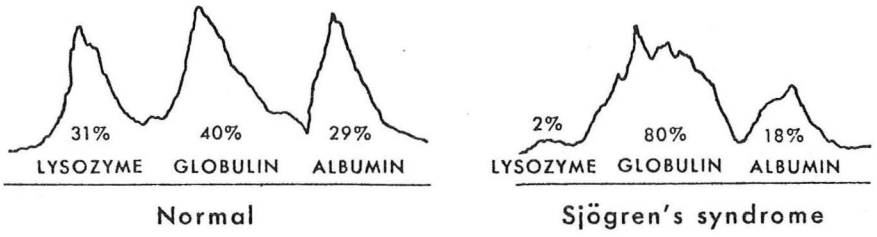

Figure 4. Normal tear electrophoresis compared with pattern in Sjögren's syndrome (15).

van Bijsterveld (20) studied the concentration of lysozyme in 43 patients with SS and 550 normal subjects using the degree of lysis of *m. lysodeikticus* as the assay for lysozyme. The results shown in Figure 5 indicated an excellent separation between normal and diseased populations suggesting that this test may be more specific for Sjögren's syndrome than the Schirmer on rose bengal tests. As a matter of fact, quantitation of lysozyme compared favorably to the information obtained from the combined results of the other two tests.

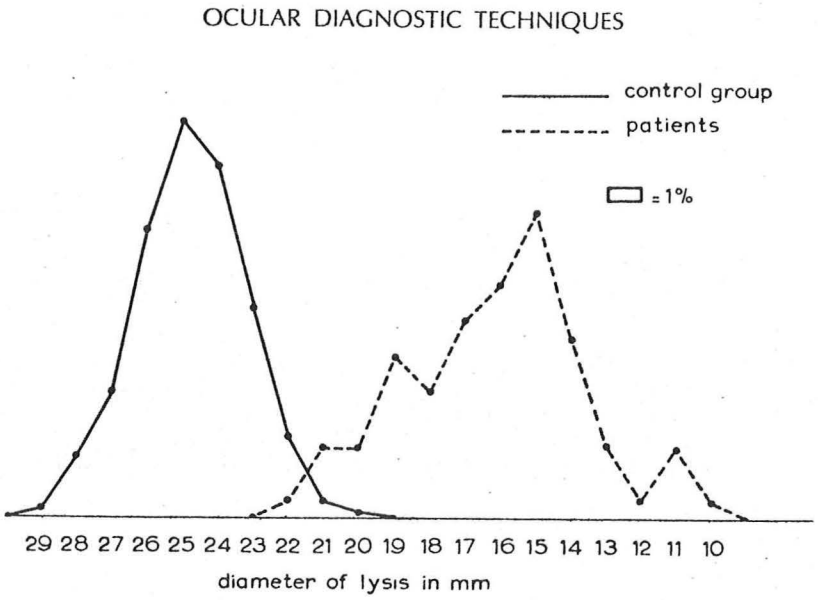

Figure 5. Concentration of lysozyme from tears of 43 patients with SS compared with that in 550 controls (20).

The major disadvantages as a diagnostic method is related to the nonavailability of the test as a routine procedure, however, a test for the quantitation of lysozyme is now commercially available.

Oral Manifestations. The most common symptom associated with salivary gland involvement is the complaint of dry mouth or xerostomia. In the group of 62 patients reported by Bloch (14) 90 per cent complained of dry mouth (Table VII). In a majority of patients with advanced disease, dryness interfered with mastication or required increased ingestion of fluids with and between meals. Some patients had to free adherent food fragments manually from the oral mucosal. Fifty eight per cent of the patients complained of fissuring or ulceration of the lips and mouth. In addition to the xerostomia, a number of patients will also show a marked loss of papillae of the tongue, which may also be deeply furrowed and acquire a magenta discoloration(2).

TABLE VII

SYMPTOMS ASSOCIATED WITH SALIVARY GLAND INVOLVEMENT

SYMPTOM	PER CENT
ORAL DRYNESS	90
DECREASED OR ABSENT SALIVA	81
DIFFICULTY WITH MASTICATION	66
INCREASED FLUID INTAKE WITH MEALS	63
FISSURING OR ULCERATION OF MOUTH OR LIPS	58
ORAL SORENESS	47
RELATED DENTAL SYMPTOMS	60

(From Bloch et al (14)

Dental symptoms related to oral dryness are also common. The most frequent problem consists of an increase in the frequency of dental caries which are rapidly progressive following the development of xerostomia.

Salivary gland enlargement is seen in a significant proportion of patients, particularly if careful examination is undertaken. In the group of 80 patients studied by Shearn (15), over 40 per cent offered a history of salivary gland enlargement. Parotid enlargement was the most common localization (Table VIII). The onset of swelling may be insidious or sudden, in the latter case, sudden tumescense is often associated with pain which is aggravated by eating. Pain may also be associated with the occasional complications seen in these patients; bacterial parotitis or salivary calculi.

TABLE VIII

SALIVARY AND LACRIMAL GLAND ABNORMALITIES IN EIGHTY PATIENTS

ABNORMALITY	PER CENT
PAROTID ENLARGEMENT	33
SUBMAXILLARY ENLARGEMENT	6
SUBMAXILLARY AND PAROTID ENLARGEMENT	3
LACRIMAL ENLARGEMENT	4

From Shearn (15)

It is then apparent that most patients with SS will show both lacrimal and salivary gland involvement so that the diagnosis can be made in most cases on the basis of the presence of xerostomia and its consequences.

TABLE IX

DIAGNOSIS OF SALIVARY GLAND INVOLVEMENT

SALIVARY FLOW MEASUREMENTS
SIALOGRAPHY
RADIOISOTOPIC STUDIES
BIOPSY OF ACCESSORY GLANDS

Salivary flow measurements can be performed under basal conditions or after chemical and mechanical stimulation with lemon juice and chewing gum. Bertram (23) showed that basal salivary flow depended on age, sex and state of health of the control subjects (Figure 6).

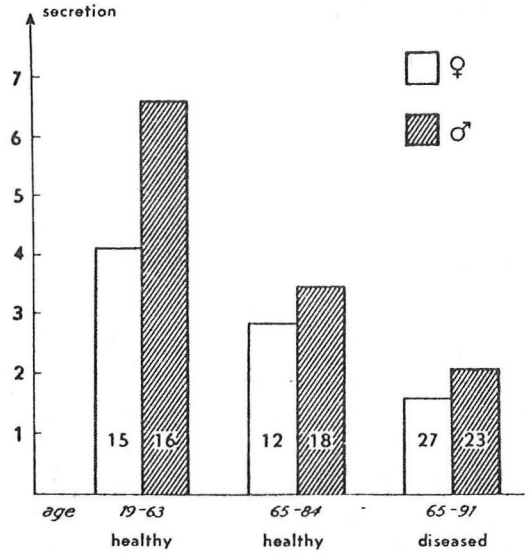

Figure 6. The effect of sex, age and state of health on salivary secretion (23).

However, in patients with xerostomia the salivary flow rate was significantly lower than that found in the healthy control group. A significant overlap was found with the group of debilitated controls, 18 of 58 control subjects secreted less than 1 ml/15 minutes which was the average flow rate in patients with intermittent xerostomia. In patients with severe xerostomia, the separation was more clear cut, the flow rate averaged 0.14 ml/15 minutes and in 50 per cent of this group the salivary flow was zero. Table X shows the correlation between the degree of xerostomia and salivary flow rates found by Bertram (23).

TABLE X

THE RELATIONSHIP OF LINGUAL CHANGES TO SALIVARY FLOW RATES IN 48 PATIENTS WITH XEROSTOMIA

LINGUAL CHANGES	MEAN SALIVARY FLOW (ml/15 mm)
Normal	1.26
Mild	0.46
Moderate	0.18
Severe	0.03

Using chemical and mechanical stimulation, Bloch et al (14) measured salivary flow in 28 patients with SS and in 12 control with rheumatoid arthritis without SS. In agreement with Bertram's findings, there was a significant decrease in flow rates in the patients with SS; it was noted further that

decrease in flow rate was more severe in patients with sicca syndrome alone, without rheumatoid arthritis.

As a diagnostic procedure, sialography is used more commonlythan salivary flow rates in most medical centers. Films are taken after instillation of the contrast medium and five minutes after the contrast material has been eliminated from the gland by the use of a sialogogue such as lemon juice. In normal sialograms, there is good definition of all ducts, including the five terminal branches of the peripheral ducts. Most of the contrast medium is completely excreted from the normal gland in less than one minute, no contrast material should be seen in the secretory phase in a normal sialogram. The abnormal patterns seen in patients with Sjögren's syndrome have been classified by Rubin and Holt (24) into four stages:

1. Punctuate- Diffuse punctuate dilation of the peripheral ducts, with narrowing of the interlobular ducts.

2. Globular- Globules of contrast material increase in size but are uniform in distribution. Appearance is termed a "mulberry pattern" or it appears as a branchless, fruit-laden tree.

3. Cavitary- Coalescence of globules, which are irregular, distorted and decreased in number, with areas of cystic dilation.

4. Destructive The pattern of the end stage is bizarre, with puddling and pooling.

The abnormal secretory phase film shows retention of the contrast material in the terminal ducts, sometimes contrast

medium can be shown in the distorted gland several days later. As shown in Table XI, the sialogram is abnormal in a very high proportion of patients regardless of whether the glands are enlarged or not.

TABLE XI

ABNORMAL SIALOGRAM IN PATIENTS WITH SJÖGREN'S SYNDROME

STUDY	NO. OF PATIENTS	PER CENT POSITIVE	REFERENCES
SILBERGER et al.	33	94	25
GONZALES et al.	63	94	26
BLOCH et al.	37	97	14
MACKENZIE et al.	93	92	27

In spite of its high degree of specificity and sensitivity, sialography has several disadvantages which should be mentioned. The procedure is not entirely innocuos, it can cause pain and swelling of the gland, oedema and allergic reaction can also occur. In addition, the procedure requires a worker trained in catheterization of the salivary ducts.

A promising non-invasive technique for evaluation of the salivary glands is scanning with technetium 99m (^{99m}Tc). The technique is based on the observation by Freinkel and Ingbar (28) that salivary gland ductal epithelium actively transports iodide into saliva, concentrating the ion 30 or 40 times. The same

phenomenon occurs with ^{99m}Tc, concentration of the isotope produces a bright image on the scintiscan. Salivary gland involvement results in a failure to concentrate ^{99m}Tc appropriately. Alarcon-Segovia et al (29) applied this method in 28 patients with Sjögren's syndrome by measuring radioactivity in saliva at 15 and 60 minutes after the intravenous infusion of the isotope. An abnormal pattern of secretion was found in 25 out of the 28 patients. These authors also pointed out that it was possible to detect changes in uptake either spontaneously or after treatment with corticosteroid therapy in patients tested repeatedly. The same group subsequently attempted to compare the sensitivity and diagnostic accuracy of radioiodide and sialographic studies in the detection of salivary gland involvement in 150 patients with connective tissue diseases commonly associated with Sjögren's syndrome (30).

TABLE XII

COMPARISON OF ^{99m}Tc UPTAKE AND SIALOGRAM IN 150 PATIENTS WITH CONNECTIVE TISSUE DISEASES

^{99m}Tc UPTAKE	SIALOGRAM: ABNORMAL	SIALOGRAM: NORMAL
ABNORMAL	4	17
NORMAL	5	124

FROM ALARCON–SEGOVIA

Seventeen patients had abnormal radionuclide scans despite a normal appearance with sialography. In 12 of these 17 patients a lip biopsy was performed and in 11 it was found to be abnormal. Conversely, an abnormal sialogram was found in 4 patients with normal scans and in 3 the lip biopsies were also abnormal. Schall et al (31) confirmed these findings in 20 patients with Sjögren's syndrome. They attempted to correlate their results with sialography, measurement of salivary flow rates and lip biopsies. The scintigraphic findings closely paralleled the results of the salivary flow-rate determinations, sialography and clinical findings. On the other hand, the lip biopsy findings suggested more serious disease that was apparent on the function tests. These authors also pointed out that the scintiscan was useful in monitoring the improvement in salivary gland function with therapy. These results are summarized in Figure 6.

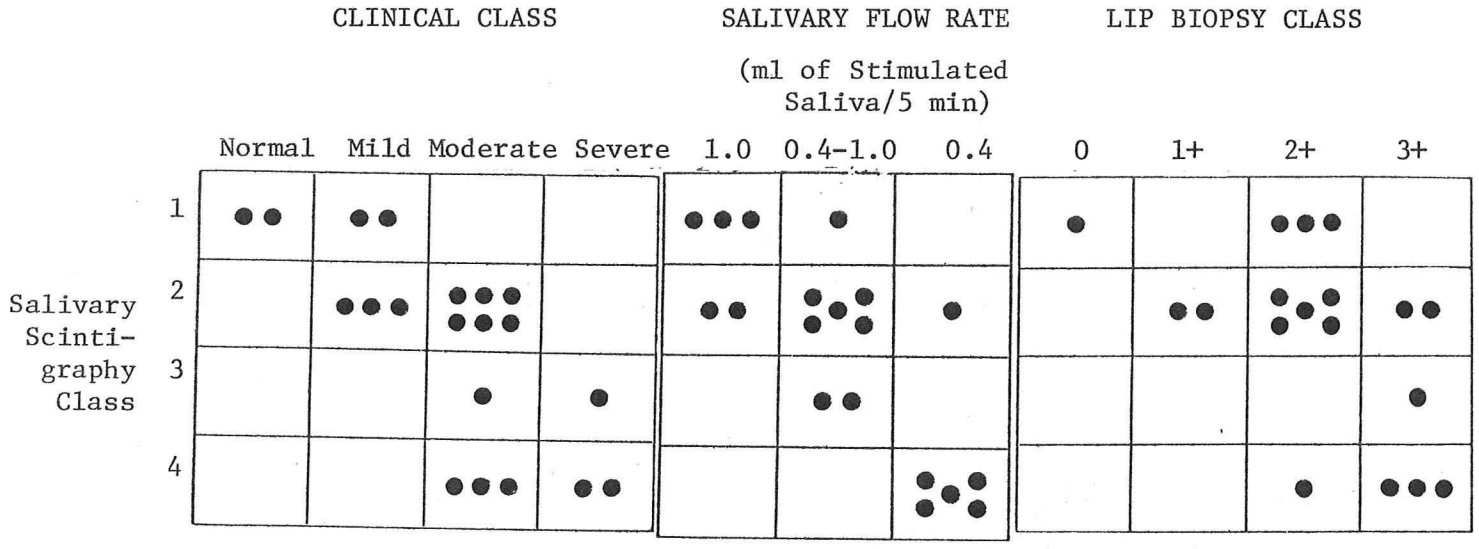

Figure 6- Correlation between scintigram and other tests used to assess salivary gland involvement.

In summary, sequential salivary scintigraphy appears to be an easy, sensitive and safe means of evaluating xerostomia in patients with SS.

The techniques discussed above give significant information but do not confirm the diagnosis of SS. Salivary gland biopsy can provide the definite diagnosis in a great majority of cases. Table XIII lists the major pathologic findings, the presence of "epimyoepithelial islands" and hyperplasia of the ductal lining cells in a biopsy is considered definite diagnostic evidence for Sjögren's syndrome.

TABLE XIII

SALIVARY GLAND PATHOLOGY

PARENCHYMAL AND DUCTAL ALTERATIONS
DECREASE OR DISAPPEARANCE OF ACINI
HYPERPLASIA OF LINING CELLS OF INTRAGLANDULAR DUCTS
FORMATION OF "EPI-MYOEPITHELIAL ISLANDS"
LYMPHOID-CELL INFILTRATION

In clinical practice, there have been several reasons to account for the difficulty in obtaining parotid gland biopsies. Parotid enlargement is clinically evidence in fewer than one-third of the cases and if reservations are held against open biopsy of an enlarged gland, there is greater reluctance to carry out this procedure on glands that appear to be of normal size. Other frequent objections include the possibility of establishing a salivary fistula and of injury to the facial nerve.

Within the last few years an important development has simplified this problem. In 1968, Chisholm and Mason (32) reported results of biopsy of the lower lip, an excellent and easily accessible site for minor salivary glands. It would appear that the minor salivary glands are involved in this general polyglandular disease but it should be emphasized that the more specific "epi-myoepithelial islands" are rarely seen in lip biopsies. However, the finding of decrease in glandular tissue and presence of lymphocytic infiltration within a pertinent clinical framework would be highly suggestive of the diagnosis.

The diagnostic value of each of the procedures described can be better appreciated in a study of 50 patients with xerostomia by Whaley et al (19) shown in Table XIV.

TABLE XIV

COMPARISON OF DIAGNOSTIC PROCEDURES IN FIFTY PATIENTS WITH XEROSTOMIA

METHOD	PER CENT POSITIVE
PAROTID SALIVARY FLOW RATES	90
PAROTID SIALOGRAPHY	62
LIP BIOPSY	72

Modified from Whaley et al (19).

Connective Tissue Diseases Associated With Sjögren's Syndrome. Connective tissue diseases occur commonly in association with the sicca syndrome. As previously mentioned, rheumatoid arthritis is present in about one-half the patients in most major series, but all the other connective tissue diseases have been reported in association with Sjögren's syndrome (15,33). Table XV shows the prevalence of this association in 80 patients studied by Shearn (15).

TABLE XV

ASSOCIATED DISORDERS IN 80 PATIENTS WITH SJÖGREN'S SYNDROME

DISEASE	PER CENT
RHEUMATOID ARTHRITIS	30
RAYNAUD'S PHENOMENON	21
CHRONIC PULMONARY FIBROSIS	15
ARTHRALGIA	10
LIVER DISEASE	6
SYSTEMIC LUPUS ERYTHEMATOSUS	5
SCLERODERMA	5
PURPURA HYPERGLOBULINEMIA	5
CHRONIC THYROIDITIS	4
MYOPATHY	3

From Shearn (15)

It is of interest that the spontaneous animal model for systemic lupus, the NZB/W mouse also offers a natural model of Sjögren's syndrome. In a study by Kessler (34),

the salivary and lacrimal glands of mice four months or older showed mononuclear cell infiltration in 100 per cent of the animals studied.

From Table XV it can be appreciated that since SS so commonly co-exists with various connective tissue diseases, one may expect to find a wide variety of symptoms and signs corresponding to the organ system involved. But even in the absence of such diseases, patients with SS may manifest an astonishing array of abnormalities. We shall discuss the organ systems most commonly involved excluding the manifestations directly related to the presence of a well defined connective tissue disease.

Cutaneous Manifestations. Skin dryness is a common manifestation of Sjögren's syndrome. Scaling is seen in 25 per cent of patients, sweating is often diminished and hair may be dry and sparse. Skin biopsy may show infiltration of the sweat glands with mononuclear cells (35, 36). The appearance of the skin may suggest hypothyroidism which is not uncommonly associated with Sjögren's syndrome, but such cutaneous changes are certainly seen in euthyroid patients. Nonthrombocytopenic purpura may occur usually associated with two clinical entities, idiopathic mixed cryoglobulinemia (37) and perhaps more commonly with benign purpura hyperglobulinemia of Waldenstrom (38). It has been estimated that 20 to 30 per cent of patients with this form of purpura have Sjögren's syndrome (39). Vasculitic lesions may occur independently

of the presence of rheumatoid arthritis or SLE, but they often resemble the lesions of rheumatoid vasculitis. Painless nail-fold infarcts, which may be transient, and splinter hemorrhages are often seen. Severe vasculitis with gangrene has been reported in a small number of patients (15).

Raynaud's phenomenon is not infrequently seen, even in the absence of a coexisting rheumatic disease (40,41). In a series of 80 patients with Shearn (15), 7 patients had isolated Raynaud's phenomenon. The cutaneous manifestations of Sjögren's syndrome are summarized in Table XVI.

TABLE XVI

CUTANEOUS MANIFESTATIONS OF SJÖGREN'S SYNDROME

DRYNESS, SCALINESS, DECREASED SWEAT
PURPURA
VASCULITIS
RAYNAUD'S PHENOMENON

Respiratory Tract Manifestations. Upper respiratory tract disease is present in Sjögren's syndrome usually associated with dryness of the upper airways. Crusting of the nasal mucosal, chronic sinusitis and otitis and persistent hoarseness are frequently reported (11). Bronchitis sicca usually accompanies the other manifestations of the syndrome, the patients complain of great difficulty in expectorating and

they have persistent cough and severe recurrent bronchitic attacks.

The pulmonary manifestations occurring in Sjögren's syndrome are similar to those seen in patients with concomitant connective tissue diseases (Table XVIII).

TABLE XVII

LOWER RESPIRATORY TRACT MANIFESTATIONS IN SJÖGREN'S SYNDROME

IDIOPATHIC PULMONARY FIBROSIS
NODULAR PARENCHYMAL DISEASE
PLEURISY WITH OR WITHOUT EFFUSION
RECURRENT INFECTIONS

Diffuse idiopathic pulmonary fibrosis is commonly present in patients with rheumatoid arthritis, SLE, or Raynaud's syndrome with or without scleroderma. The coexistence of the sicca syndrome with pulmonary fibrosis has been reported by several authors (15,42, 43). Mason et al.(44)reported nine patients with the sicca syndrome, fibrosing alveolitis and renal tubular acidosis, none of whom had coexisting connective tissue disease. Pulmonary function studies show a restrictive ventilatory defect with decreased lung compliance and impaired diffusing capacity (15,45). Ventilation-perfusion imbalance has also been reported. Lung pathology

consists of thickening of the alveolar septa with lymphocyte and plasma cell infiltration of variable degree and fibrosis. Deposition of immune complexes in such lesions has been shown by immunofluorescence (46). A picture of primary pulmonary hypertension has also been described in some patients (47). This group has a high incidence of clinical and laboratory abnormalities associated with connective tissue disease such as Raynaud's phenomenon and rheumatoid factor in serum.

Nodular parenchymal disease is found infrequently, and usually in association with rheumatoid arthritis. Occasionally, nodules have been observed in the absence of rheumatoid arthritis or in an anarthritic individual in whom peripheral features of rheumatoid arthritis arise subsequently (48).

There are many factors present in patients with Sjögren's syndrome that predispose to recurrent pulmonary infections. We have already discussed the extreme dryness of the respiratory tract, additional mechanisms include a reduction in the concentration of IgA as a consequency of mucosal glandular involvement and the state of spontaneous or therapy-related immunosuppression so frequently encountered in these patients.

Skeletal Muscle Manifestations. Myositis appears to be a fairly common characteristic of SS. Muscle biopsies performed in patients without overt symptoms or signs of muscle disease often show myositis (49) of the same degree found in asymptomatic patients with rheumatoid arthritis. The association with clinically apparent polymyositis occurs frequently

(50-52), several authors consider that those cases with sicca syndrome with clinical polymyositis form a specific group (14). Denko and Old (53) detected a pathologic feature which they claimed is characteristic of the myopathy of Sjögren's syndrome. In 12 of 23 patients a characteristic subsarcolemmal microcystic change was detected within the muscle bundles when the sections were cut longitudinally. It should also be emphasized that myositis of variable degree is part and parcel of most of the connective tissue diseases associated with Sjögren's syndrome including the mixed connective tissue disease syndrome described by Sharp (54) and reported by Alarcon-Segovia (55) to have an incidence of concomitant Sjögren's syndrome as high as 48 per cent.

Gastrointestinal Manifestations.

Dysphagia is a common complaint in Sjögren's syndrome, and in some series it has been noted to occur in over 30 per cent of the cases (56, 57). Several causes contribute to make this a common symptom. Dysphagia may be due to the difficulty in forming the bolus because of the absence of saliva and of dryness of the esophageal mucosa. Atrophy of the esophageal mucosa has been noted by Hradsky et al. (58) with atrophy of the glands and replacement of the acini by chronic inflammatory cells. The presence of esophageal webs and postcricoid narrowing has also been reported (57,58). In addition, dysphagia may be secondary to an abnormal

esophageal motility in patients with concomitant Raynaud's phenomenon or to pharyngeal muscle weakness in patients with myositis.

Clinically inapparent atrophic gastritis and achlorhydria are a common feature in Sjögren's syndrome. Stoltze et al. (56)detected achlorhydria in 6 of 36 patients, McLenachan (59) found it in 3 of 10 patients and hypochlorhydria in the remainder. Gastroscopic examination show mucosal atrophy which often has a cobblestone appearance (60). In spite of the common finding of achlorhydria, atrophic gastritis, and pariental cell antibodies (61) in these patients, there is no increase in the incidence of pernicious anemia and serum B12 levels are usually normal (61). Williamson et al. (62) studied 77 patients with pernicious anemia for the presence of sicca syndrome. There was no significant difference between the prevalence of abnormalities in those patients and a hospitalized control group.

Clinically apparent hepatobiliary disease has not been widely observed in Sjögren's syndrome. Hepatomegaly has been reported in 18 to 23 per cent of the patients (63) and abnormal liver function tests have been found in about 15 per cent of the cases (14,63). In the group of 80 patients studied by Shearn (15), primary biliary cirrhosis was found in 3 patients and in 2, the diagnosis of chronic hepatitis was made. Although there was some selection in the sample, he concluded that the association was a real one. On the

other hand, the incidence of Sjögren's syndrome in patients with chronic liver disease is quite high. Krook (64) found that 5 of 9 patients with liver disease had SS; in 63 patients investigated by Golding (65), the sicca syndrome was diagnosed in 42 per cent with chronic active hepatitis, 72 per cent with primary biliary cirrhosis and 38 per cent with "cryptogenic cirrhosis". Doniach and Walker (66) have applied the term "autoimmune liver disease" to these three disorders and the sicca syndrome was detected in 51 per cent of all the patients investigated. Thus, patients with chronic liver disease have high incidence of sicca syndrome, but it is unlikely to be diagnosed unless specifically looked for because the ocular and oral symptoms are overshadowed by the systemic disturbance.

TABLE XVIII

GASTROINTESTINAL MANIFESTATIONS IN SJÖGREN'S SYNDROME

ORGAN	MANIFESTATION	ASSOCIATED FINDING
ESOPHAGUS	DYSPHAGIA	MUCOSAL ATROPHY RAYNAUD'S PHENOMENON POLYMYOSITIS
STOMACH	ACHLORHYDRIA	ATROPHIC GASTITIS
PANCREAS	DECREASED SECRETION	LYMPHOCYTIC INFILTRATION
LIVER	PRIMARY BILIARY CIRRHOSIS CHRONIC ACTIVE HEPATITIS "CRYPTOGENIC CIRRHOSIS"	

Thyroid Disease. The association of clinical thyroid disease with SS has been recognized by a number of authors (14,15,56,60,63,67). The incidence of significant thyroid dysfunction has been reported to be about 10 per cent in two large series of patients (14, 15). Thyroid enlargement may be as common, it was present in 13 per cent of the patients in Shearn's series (15). The association of Hashimoto's thyroiditis with Sjogren's syndrome has been looked at by several workers because of the many common features of the two diseases; i.e. female predominance, hypergammaglobulinemia, high incidence of autoantibodies, etc. In two large series with an aggregate of 142 patients (14,15) with SS the incidence of Hashimoto's thyroiditis was 4 per cent. No definite conclusion can be reached as to this association since there has been no systematic study of thyroid dysfunction in SS patients and age and sex-matched controls. The reverse situation has been looked at by Williamson et al. (68) who determined the prevalence of sicca syndrome in patients with autoimmune thyroid disease and a group of hospital out-patient controls. They found no difference between the two groups even though the controls were not matched for age and sex.

Autoantibodies to thyroid components are commonly found. Bloch and Bunim (11) detected antithyroblobulin antibodies in 35 per cent of their patients but none showed the high titers usually seen in patients with Hashimoto's thyroiditis. Anderson et al. (69) found 42 per cent positive tests for

thyroid autoantibodies in their group of patients.

Renal Manifestations. Renal abnormalities are found with great frequency in patients with Sjögren's syndrome and most of these consist of abnormalities in renal tubular function. In 1958, Gordon and Shambron (70) first reported a patient with inability to concentrate urine above a specific gravity of 1010. Kahn et al. (71) selected eight patients with SS who were unable to concentrate urine above 1018 in random overnight specimens and found four that had a defect in urine concentration. Four of eight patients studied by Bloch et al. (14) were found to be unresponsive to vasopressin and Shearn and Tu (72) found four patients with a concentration defect in the ten unselected cases they studied. Many of the patients with xerostomia may frequently drink large amounts of fluids resulting in a secondary hyposthenuria as a result of a diminution of the osmolar gradient in the concentrating segment of the nephron. Retesting the patients after prolonged water restriction confirmed the primary nature of the tubular abnormality. The other major abnormalities frequently found in patients with Sjögren's syndrome is that of complete or incomplete renal tubular acidosis. Shearn and Tu (72) reported a patient with nephrogenic diabetes insipidus and renal tubular acidosis. Subsequently, the same authors found 3 cases of incomplete renal tubular acidosis in 10 unselected cases of Sjögren's syndrome. Morris and Fudenberg (73) recorded

2 of 3 patients with tubular acidosis. Finally, Mason and Golding (74) studied nine patients with both renal tubular acidosis and sicca syndrome, four of them with overt acidosis and seven with nephrogenic diabetes insipidus. A small number of patients has also been reported to have proximal tubular defects and the Fanconi syndrome (72,75). Thus, tubular defects appear to be quite common in Sjögren's syndrome; from the relatively small number of cases reported it may be that up to 30 per cent of all patients may have a tubular defect. It is also apparent that the distal tubule is affected much more commonly than the proximal.

TABLE XIX

RENAL MANIFESTATIONS IN SJÖGREN'S SYNDROME

NEPHROGENIC DIABETES INSIPIDUS
RENAL TUBULAR ACIDOSIS (TYPE I)
RENAL TUBULAR ACIDOSIS (TYPE II)

The observation of a high gammaglobulin concentration in many of the diseases in which renal tubular acidosis is found has prompted speculation as to whether it is the high gammaglobulin per se that is pathogenetically related to the tubular defect. Both Shearn and Tu (76) and Shioji et al. (77) failed to show a correlation between the severity of the tubular defect and gammaglobulin concentration. In addition, studies in patients with rheumatoid arthritis with-

out Sjögren's have failed to show increased incidence of tubular acidosis (78).

The single consistent abnormality found in the renal biopsy specimens of these patients is chronic interstitial nephritis. The infiltrate consists mostly of lymphocytes and plasma cells and fibrosis may be prominent. Although the interstitial infiltrate may be present in the absence of tubular dysfunction, most patients with tubular acidosis will have evidence of interstitial nephritis or fibrosis.

Hematologic Manifestations. In some patients with SS, the tissue infiltration with lymphoid cells is found not only in glandular structure but also in lymphnodes, bone marrow, muscle and other organs. "Pseudolymphoma" (80) is a term that is applied when the lymphoid cell infiltrate occurs in sites other than the exocrine glands but it does not meet the histological criteria for malignancy, usually by lack of invasive features. The most common clinical presentation is that of generalized lymphadenopathy, but single organs such as lung and kidneys may also be involved. Anderson and Talal (79) have reviewed the clinical features of eight patients with this entity. They have pointed out that these patients have a higher incidence of leukopenia, purpura, vasculitis and neuropathy as seen in Table XX. In addition, progression to lymphoma or macroglobulinemia is common.

TABLE XX

CLINICAL FEATURES OF PATIENTS WITH SJÖGREN'S SYNDROME WITH AND WITHOUT EXTRASALIVARY LYMPHOID ABNORMALITIES

CLINICAL FEATURES	WITH	WITHOUT
XEROSTOMIA	100	88
SALIVARY GLAND ENLARGEMENT	100	50
KERATOCONJUNCTIVITIS SICCA	82	89
LYMPHADENOPATHY	77	0
SPLENOMEGALY	77	23
LEUKOPENIA	77	26
PURPURA	62	4
VASCULITIS	54	22
NEUROPATHY	31	2

From Talal et al (80)

It is now well established that malignant lymphoma may complicate the course of SS (79). Since the early observation by Rothman (81) over 30 cases have been reported. The two malignant disorders most commonly seen are reticulum cell lymphoma and Waldenstrom's macroglobulinemia, less frequently. Giant cell follicular lymphosarcoma, Hodgkin's disease and thymoma have been reported.

TABLE XXI

LYMPHOID CELL ABNORMALITIES IN SJOGREN's SYNDROME

"PSEUDOLYMPHOMA"
RETICULUM CELL SARCOMA
WALDENSTROM'S MACROGLOBULINEMIC

IV. IMMUNOLOGIC ABNORMALITIES

The enormous incidence of immunologic abnormalities is one of the most striking features of SS. In 1958, Jones (82) first demonstrated antibodies to extracts of salivary and lacrimal glands and in the same year, Weissmann (83) reported rheumatoid factor activity in a patient with SS. Since then, a number of investigators have documented the high incidence of autoantibodies in patients with and without connective tissue disease.

Humoral abnormalities. Patients with SS frequently show diffuse elevations of serum gamma globulin or electrophoresis (14, 15). Measurements of immunoglobulin classes have shown elevation in IgG, IgA, and IgM. As mentioned above, monoclonal spikes of the IgM class are not uncommonly seen. Hypogammaglobulinemia and a drop in autoantibody titers has been observed in association with the development of reticulum cell sarcoma.

TABLE XXII

RHEUMATOID AND ANTINUCLEAR FACTORS IN PATIENTS WITH SJÖGREN'S SYNDROME

	SS WITH CONNECTIVE TISSUE DISEASE %	SICCA SYNDROME
RHEUMATOID FACTOR	75-100	48-95
ANTINUCLEAR FACTOR	50-75	33-85

One of the most striking findings included in the classic work by Bunin and his associates from the NIH (14) was the very high incidence of positive rheumatoid factor tests both in SS patients with and without associated connective tissue diseases (Table XII). Subsequent series confirmed this finding (63,84) but when less severely involved patients are included, the proportion of patients with sicca syndrome with positive rheumatoid factor tests tends to decrease. A similar observation has been made with respect to the presence of antinuclear factors. Positive LE preparations have been reported in about 15 per cent of the patients, the majority with associated SLE or rheumatoid arthritis (15,63). Antinuclear factors are detected with frequencies approaching those found in patients with SLE (14,84) and as it is the case for

rheumatoid factor, the patients with sicca syndrome are positive in a high proportion. The most common nuclear fluorescence patterns reported are; diffuse, speckled and nucleolar. The antibody specificities have been sparsely studied; most of the activity is directed against single stranded DNA or other nucleoprotein nuclear antigens (85)

Antibodies to tissue extracts have been frequently detected in patients with SS. Jones (82) first demonstrated the presence of antibodies to extracts of lacrimal and salivary glands in patients with SS. It was subsequently shown that the antibodies were not specific since they reacted with a variety of extracts of both human and animal tissues such as thyroid, kidney spleen, adrenal gland and brain (69). Salivary duct antibody was found in 70 per cent of patients with SS by Bertram and Halberg (86). This antibody is specific for salivary and lacrimal duct epithelium, there is no cross-reaction with other glandular epithelium. It appeared initially to be a useful diagnostic test, but subsequent studies (87,88) have shown that the antibody is found almost as commonly in patients with uncomplicated rheumatoid arthritis as in those with SS. One of the surprising recent developments in the study of SS derives from this type of investigation of the specificity of the autoantibodies present in SS. The incidence of antibodies to salivary duct epithelium was found to be much higher in patient with concomitant rheumatoid arthritis than in patients with sicca syndrome alone (88).

Recently, Alspaugh et al (89) studied the precipitating antibodies to an extract of lymphoblastoid cells and found two systems called SS-A and SS-B that gave positive reactions in 70 and 48 per cent of patients with sicca syndrome and only 9 and 3 per cent in patients with SS and rheumatoid arthritis. These findings have been confirmed by others (90).

TABLE XXIII

FREQUENCY OF PRECIPITINS SS-S AND SS-B IN CONNECTIVE TISSUE DISEASES

DISEASE	PER CENT POSITIVE	
	SS-A	SS-B
SICCA SYNDROME	70	48
SS-RHEUMATOID ARTHRITIS	9	3
SLE	0	0
SCLERODERMA	0	1
RHEUMATOID ARTHRITIS	0	0

From Alspaugh et al (89).

These findings suggest that mechanisms involved in the generation of the clinical pathological entity known as Sjögren's syndrome may be different in the group of patients

with sicca syndrome.

Cellular Immunity. In addition to abnormalities of the humoral immune system, cell mediated immunity has been shown to be impaired in patients with SS. Leventhal et al. (91) and Whaley et al. (88) showed that there was an impaired reactivity of peripheral blood lymphocytes to T-cell mitogens. Furthermore, the capacity of these patients to develop delayed hypersensitivity to a contact allergen; 2, 4 DNCB was impaired. It is of interest that these studies also suggested a difference between groups; impaired reactivity was more prevalent in patients with SS and rheumatoid arthritis or pseudolymphoma than in patients with sicca syndrome alone.

The nature of the lymphocytes infiltrating the salivary glands has also been the subject of investigation. Anderson et al. (92) demonstrated local synthesis of large amounts of immunoglobulins and rheumatoid factor in salivary gland tissue of patients with SS. The nature of the small lymphocyte infiltrating the glands is unsettled. Tannembaum et al. (93) and Talal et al. (94) suggested that the predominant monoclear cell in salivary glands was the T-lymphocyte whereas Chused et al. (95) showed that a large number of infiltrating small lymphocytes exhibited C3 receptors on their cell membrane thus indicating their B-lymphocyte nature.

The intensity of the lymphoid cell infiltrate of the salivary glands can be determined by non-invasive means

by measuring the concentration of $Beta_2$ microglobulin in saliva. This low molecular weight protein is a constituent of cell membranes and is secreted by lymphocytes. Michalski et al. (96) found a very good correlation between the salivary concentration of $Beta_2$ microglobulin and the degree of inflammation seen in the lip biopsy in 49 patients. The concentration decreased in 6 after clinically efficacious therapy.

V. GENETIC STUDIES

Perhaps the strongest indication that there may be a fundamental difference between patients with sicca syndrome alone and SS with rheumatoid arthritis originates in the recently published genetic studies. Early work suggested that there may be some familial aggregation in SS. Lisch (97) reported a family in which three generations had SS with 11 of 13 members of the third generation being affected. Bloch et al. (14) showed an increased incidence of rheumatoid arthritis, autoantibodies, gamma globulin concentration and tear formation as compared to next-door neighbor age, sex and race-matched controls. Fye et al. (98) found an increased incidence of HLA-B8 in patients with SS, the same tissue antigen that has been linked to coeliac disease, dermatitis herpetiformis, myasthenia gravis, Grave's disease chronic active hepatitis and juvenile diabetes mellitus. The

authors suggest that HLA-B8 is genetically linked to immune response genes that predispose to autoimmune phenomena. Recently, Chused et al. (99) found a striking prevalence of HLA-B8 and HLA-Dw3 in SS patients. HLA-Dw3 was observed in 84 per cent of patients with SS in the absence of rheumatoid arthritis as compared to 24 per cent in controls, the frequency of HLA-B8 and HLA-Dw3 in patients with SS and rheumatoid arthritis did not differ from that in controls. Thus, patients with SS alone and those with SS and rheumatoid arthritis comprise genetically distinct groups.

TABLE XXIV

HLA-B8 and HLA-Dw3 DETERMINANTS

IN PATIENTS WITH SJÖGREN'S SYNDROME

	B8+	B8-	Dw3+	Dw3-
SICCA SYNDROME	74	26	84	16
SS WITH RHEUMATOID ARTHRITIS	0	100	17	83
CONTROLS	21	79	24	76

VI. TREATMENT

The single most effective measure that will produce symptomatic improvement in a majority of patients is the replacement of tears with buffered methyl-cellulose solutions. When excess mucus is a problem addition of 10 per

cent acetylcysteine to the artificial tears may be helpful. Eyeglasses should be worn whenever possible to protect the eyes from foreign bodies and reduce the rate of evaporation of tears from the conjunctival sac.

Xerostomia is more difficult to treat, frequent sips of water often give symptomatic relief. Sialogogues have not proved to be of any value but in the early stages lemon or citric acid drops may be useful to stimulate salivary secretion. Ehrlich (100) has described the "sour-ball sign": "Connective tissue disease plus sour-ball or hard candy at the bedside equals Sjögren's syndrome." Careful dental and gum care with frequent brushing to remove food particles is extremely important to prevent the rapid appearance of dental caries and secondary infections.

Parotid enlargement seen in about one third of the patients occasionally respond to corticosteroid therapy. Sudden enlargement with associated pain may be due to calculi obstructing the major salivary ducts and these should be removed surgically. Otherwise, every effort should be made to preserve glandular tissue. Local x-radiation is contra-indicated, Anderson and Talal (79) reported that irradiation had been administered to the salivary glands in three of their patients before the development of malignant lymphoma and macroglobulinemia.

Associated connective tissue diseases should be treated as in patients without SS. Patients with rheumatoid arthritis

and SS respond in the same fashion as those without SS to such agents as gold salts and antiinflammatory drugs. Corticosteroids are indicated in patients with myositis, hemolytic anemia or pulmonary fibrosis.

Severe complications have been treated with cytotoxic agents with apparent improvement in salivary gland function (15). These are isolated reports, no control studies are available, and since SS patients are prone to the development of malignancies, the use of these agents should be generally avoided.

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