

Sjögren's Syndrome

A Review with Emphasis on Immunological Features

R. MANTHORPE¹, K. FROST-LARSEN², H. ISAGER³ and J. U. PRAUSE⁴

¹Medical Dept. TA, State University Hospital, ²Eye Dept., Gentofte University Hospital, ³Dept. of Infections Diseases, State University Hospital and ⁴Eye Pathology Institute, University of Copenhagen, Copenhagen, Denmark

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HISTORY

The combination of reduced salivary secretion and lack of lacrimal gland secretion was reported by Hadden in 1888 (25). In 1925 Gougerot (23) described three patients with progressive atrophy of the salivary glands and the mucous glands of the conjunctiva, mouth, nose, larynx and vulva. Henrik Sjögren, in his comprehensive monograph from 1933 (58), combined the clinical and pathological findings into a single entity. He introduced the term keratoconjunctivitis sicca for the eye symptoms. The eponym, Sjögren's syndrome (SS), is now commonly used in appreciation of his extensive publications on the subject.

Holm, (30) further emphasized the association between lacrimal and salivary dysfunction and the rheumatological disorder. The concept

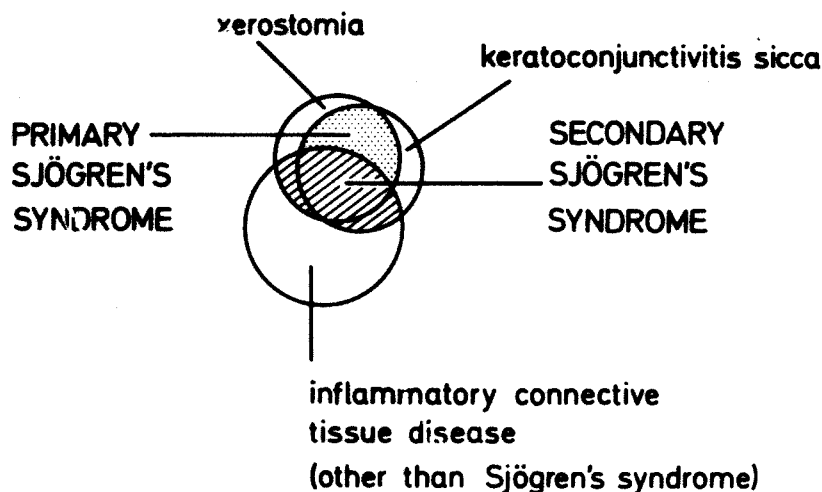
of SS has changed from being an ophthalmological curiosity, to the current concept of being the next most common disease of the chronic inflammatory connective tissue associated with general affection of the exocrine glands, probably of autoimmune origin.

Within the last decade contemporary knowledge of the syndrome has been summarized by Shearn (57), and recently by Whaley & Buchanan (67) and Moutsopoulos et al (48).

DEFINITION

In Sjögren's description of the syndrome (58) the patients presented had keratoconjunctivitis sicca, xerostomia and "arthritis". Later it became evident that many rheumatological diseases

Fig. 1.



may be seen in combination with keratoconjunctivitis sicca and xerostomia (Fig. 1). Accordingly, SS is defined by the presence of at least two of the following three criteria (9):

- 1) keratoconjunctivitis sicca,
- 2) xerostomia and
- 3) another well-defined chronic inflammatory connective tissue disease.

SS is classified as primary when only the first two criteria (1 and 2) are fulfilled, and as secondary when the third is present (Fig. 1).

In the literature the term "sicca syndrome" or "sicca complex" is often used to describe the presence of 1 + 2 only. As patients with or without 3 may feel equally dry the term "sicca" is to be avoided. We therefore introduced the classification of primary SS and secondary SS (20), where primary SS may be considered synonymous with the older term.

Rheumatoid arthritis is the connective tissue disease most frequently associated with SS, but SS may also be found in patients with systemic lupus erythematosus, progressive systemic sclerosis, mixed connective tissue disease, polymyositis, and other chronic inflammatory connective tissue diseases.

Keratoconjunctivitis sicca is defined by the presence of at least two abnormal tests among the following three:

- 1) Schirmer test,
- 2) break-up time and
- 3) van Bijsterveld score (quantitative rose-bengal dye test).

The tests are described on p. 141.

Xerostomia is defined by the presence of at least two abnormal tests among the following three:

- 4) lower lip biopsy,
- 5) sialometry and
- 6) salivary gland scintigraphy.

Sialography may replace salivary gland scintigraphy. For description of the tests see p3-4

By introducing the criteria of at least two characteristic abnormal results out of three tests performed for one organ, we avoid the error of relying on a single test in the diagnosis of keratoconjunctivitis sicca and/or xerostomia. As discussed among others by Shearn (57) and Whaley & Buchanan (67) the latter has been shown to be misleading. Further, we continue the tradition of making the diagnosis of keratoconjunctivitis sicca as simple and reliable as that for xerostomia (7).

EPIDEMIOLOGY

The true prevalence of Sjögren's syndrome is unknown as many cases probably remain undiagnosed, but Sjögren's syndrome is considered the next most common of the various chronic inflammatory connective tissue diseases (48, 57) only rheumatoid arthritis being more frequent. It is generally accepted that about half of the SS cases are primary, the other half being secondary SS. In rheumatoid arthritis 25–50% of the patients fulfil the criteria for secondary SS.

As with most of the other chronic inflammatory connective tissue diseases SS occurs mainly in women, the female/male ratio being 9:1.

The disease may develop during childhood,

but the onset most frequently occurs in adult age with a peak between 40 and 60 years (9, 39, 57).

KERATOCONJUNCTIVITIS SICCA

Tear film

The tear film is usually described as consisting of three layers (29). The outermost layer consists of lipids from the glands of Zeis and Moll. The middle aqueous layer, predominantly derived from the lacrimal glands, contains inorganic salts and trace elements, glucose, urea and macromolecules. The innermost (hydrophilic) layer is a mucous coat derived from the complex system of goblet cells (35).

Keratoconjunctivitis sicca is the most common syndrome with aqueous phase deficiency. It usually develops slowly into a chronic conjunctivitis. In severe cases, keratoconjunctivitis sicca ends as a filiform keratitis, leading to corneal ulceration and/or scarring.

Estimation of the tear flow is an essential diagnostic procedure in keratoconjunctivitis sicca. A short account of the current clinical tests is presented below. A detailed presentation of the methodological aspects has been given elsewhere (21).

Measurement of tear film disorders

As mentioned on p. 141 the Schirmer test, break-up time and van Bijsterveld score are used as diagnostic criteria.

Diagnostic criteria tests

Schirmer test. A standardized strip of blotting paper is inserted into the lower conjunctival fornix. After 5 min the strip is removed and the length of the wetted part measured from the fold. A wetting of less than 10 mm is generally considered abnormal.

The break-up time (BUT) is defined as the interval between a complete blink and the appearance of the first dry spot. Using the slit lamp, dry spots are observed as defects in the fluorescein-stained tear film.

A break-up time of more than 10 s indicates normal tear film stability (37).

Vital staining. Fluorescein/rose-bengal mixture (1%/1%) stains denuded areas of the cornea and rose-bengal stains both dead cells and partially damaged cells. The degree of the staining is estimated in the slit lamp. van Bijsterveld (8) introduced a scoring system based on the number of rosebengal stained dots, the point system ranging from 0 to 9 on each eye. A score above 4 on an eye is considered pathological.

Other ocular tests

Slit lamp examination. Permanent dry spots can be seen as a fine epithelial oedema, covered by minute filaments.

Corneal sensitivity. Corneal sensitivity is reduced in approximately 20% of patients with SS (30).

Lysozyme test. A standardized disc of blotting paper is inserted into the inferior fornix. When saturated with tear fluid, it is placed on a standardized, commercially available agar medium, which has been floated with a broth culture of *Micrococcus lysodeicticus*. After 24 h, the lytic zone caused by the lysozyme action in the bacterial cell walls is measured. In Sjögren's syndrome the lysozyme test is usually decreased (8).

XEROSTOMIA

Oral and pharyngeal dryness are typical complaints. The amount of saliva is reduced and the normal serous secretion is replaced by a thick, sticky, flocculent mucoid material. Swelling of the salivary glands is common; it is often unilateral, and may vary with disease activity.

As mentioned on p. 140 a lower lip biopsy, sialometry and salivary gland scintigraphy are used as diagnostic criteria.

Diagnostic criteria tests

A lower lip biopsy may reveal the histopathological changes typical of SS. The alterations are described on p. 142.

Sialometry. Normal and pathological values for sialometry are given in Bertram's monograph on xerostomia (7). He showed that women exhibit a lower quantity of saliva obtained by unstimulated sialometry than men. In daily practice we consider *unstimulated* values below 1.5 ml/15 min pathological unless the patient is receiving medication that affects the production of saliva.

Salivary gland scintigraphy performed with ^{99}Tc -pertechnetate may show the typical alterations with diminished uptake and reduced spontaneous secretion of the isotope as well as lack of secretion of the isotope after stimulation of the salivary glands.

The sialometry and scintigraphy are probably the functional tests most easy to perform and the least harmful to the patient (12).

Other salivary gland tests

Sialography usually show sialectasis with disappearance of the intraglandular ducts. This picture has been termed a "mulberry pattern". Other bizarre pictures may be seen in the end stage of the disease.

HISTOPATHOLOGY

Conjunctiva and cornea. Due to an inadequate amount and quality of the aqueous phase in the tear film the epithelia degenerate; this creates dry spots and hyperosmolarity. Inter- and intracellular oedema, spongiosis and cystic changes are seen, and portions of the superficial layers of the epithelia slough off resulting in corneal filaments. Areas with atrophy and dyskeratosis are found, but no true keratinization (28, 52).

The number of goblet cells is generally reported to be normal (59). If a reduction is present it is less pronounced than the corresponding reduction in aqueous production (53).

Lacrimal and salivary glands. Focal ectasia and intraductal proliferation of epithelial and myoepithelial cells are initial signs; this is followed by the gradual development of a benign lymphoepithelial lesion (8, 17, 46, 57, 67). The glandular parenchyma is replaced by an infiltrate contain-

ing mainly lymphocytes and plasma cells, and acinar atrophy develops. Proliferation of basement membrane-like material is found around and within the epimyothelial islands, which eventually are the only persisting parenchymal elements.

Studies performed by Talal et al. (64) have shown that larger lymphocytic infiltrates have centrally situated T-lymphocytes, and B-lymphocytes and plasma cells in the periphery. In small lesions only B-lymphocytes could be demonstrated (64).

SYSTEMIC MANIFESTATIONS

The following description of systemic manifestations is relevant mainly in primary SS. This disease has often – at least in its initial years – active and inactive periods. Symptoms and signs from organs outside the lacrimal and salivary glands are usually designated *extraglandular manifestations*.

Affection of secretory glands other than the lacrimal and salivary is common. The symptoms are usually due to a general atrophy of the glands in the various organs. The *skin* is dry, often with pruritus, scaling and a reduced capacity for sweating. *Vaginal dryness* can cause pruritus, dyspareunia and a burning pain. Symptoms from the *larynx*, the *bronchia* and *lungs* occur frequently. Bronchitis sicca gives rise to a dry, non-productive and tenacious cough. Migratory pulmonary infiltrations may occur. Histologically, intense lymphocytic infiltration is seen. The *gastro-intestinal tract*, *pancreas* and the *liver* may all be involved. Dysphagia, abdominal pain and diarrhoea are the main symptoms.

Other systemic manifestations which are predominating symptoms in Sjögren's syndrome are: *Universal tiredness*, the patients may rest/sleep 10–14 h or more a day. *Fever* (lowgrade) may be found during the active stages. *Arthralgia* is the most common extraglandular complaint and may precede ocular and oral symptoms by several years. X-ray alterations with erosions and destructions are rarely seen. Diffuse *myalgia* is common. A muscle biopsy may show lympho-

cytic accumulation, especially around the small vessels. The *kidney* may be involved in 15–25% of all cases. Renal function is rarely affected. The typical renal histopathological alteration is an interstitial lymphocytic infiltration with tubular atrophy and sometimes fibrosis. Immunecomplex glomerulonephritis has been described by light and electron microscopy of renal biopsies (47). Renal *tubular acidosis*, so-called nephrogenic diabetes insipidus, and rarely, aminoaciduria (Fanconi's syndrome) are also seen. *Areal alopecia* may be seen. *Purpura*, due to hypergammaglobulinaemia (Waldenström) may occur especially on the lower extremities. *Raynaud's* phenomenon is a common finding. Systemic *vasculitis* may occur in active stages of the disease but the frequency is lower than 10%. The vasculitis may give rise to mucocutaneous ulcerations. With the exception of isolated *trigeminal neuropathy*, involvement of the *central and/or peripheral nervous system* seems to be rare, in contrast to the findings observed in systemic lupus erythematosus.

Lymphoid organs

Enlargement of the axillary lymph nodes is quite common (25–50%) followed by enlargement of the nodes of the neck, spleen and inguina. In some patients, a clinical picture suggestive of malignant lymphoma develops. Histopathologically, infiltrates of lymphocytes, plasma cells and reticulum cells distort the structure of the lymph node and extend beyond the capsule (62). The distinction between benign lesion and malignancy may be very difficult. The term "pseudolymphoma" has been applied to lesions where clear evidence of malignancy is lacking (62). These lesions may also appear in non-lymphoid tissues (62, 63).

NEOPLASIA

In 1951 it was first reported that malignant non-Hodgkin lymphoma may complicate the course of SS (55). Later follow-up investigations of patients with SS have all confirmed that the frequency of malignant lymphoproliferative disorders is increased (9, 13, 62, 63). The

relative risk of developing a lymphoproliferative malignancy has been estimated to be 44 (34). However, as just mentioned there exists a wide histological spectrum of lymphoproliferation from benign to malignant disease states – with pseudolymphoma in between (5).

A fall in the level of serum immunoglobulins, usually IgM, may accompany or precede the appearance of malignancy (62). Biopsy studies from organs heavily infiltrated with lymphocytes may show monoclonal immunoglobulin markers on most lymphocytes, months before clinically frank neoplasia has developed (16).

A Canadian study (51) has shown that 25% of consecutive patients with recently diagnosed malignant non-Hodgkin lymphoma fulfil the criteria of Sjögren's syndrome. Many of the other patients had single objective findings indicating SS abnormalities. This study has not yet been confirmed by others. Future studies in SS patients may be concerned with the prediction of development of malignant non-Hodgkin lymphoma by immunological techniques, e.g. HLA-D and Ia typing.

Also in systemic lupus erythematosus the relative risk of developing a non-Hodgkin malignant lymphoma is increased. As patients with either primary Sjögren's syndrome or systemic lupus erythematosus both seem to have increased frequency of the HLA-Dw2 and/or HLA-Dw3 antigen (Table 2) it is tempting to speculate that one of these antigens may predispose to developing neoplasia in the lymphoid system. One of our patients with primary SS, who had been tissue-typed and developed a lymphoproliferative disorder, in fact had the HLA-Dw3 antigen.

LABORATORY FINDINGS

Haematology and serology

Table 1 summarizes the haematological and serological abnormalities associated with primary and secondary SS. We perform these tests while the diagnosis is being made.

Tissue typing

In the last decade, HLA-D typing of lympho-

Table 1

Prevalence of some blood abnormalities in clinically active primary and secondary Sjögren's syndrome

		Primary Sjögren's syndrome (per cent)	Secondary Sjögren's syndrome (per cent)	References
Haematological abnormalities				
Anaemia	(< 7.5 mmol/l)	25-40	50-90	14, 43, 57
Leucopenia	(< $4.5 \times 10^9/l$)	20-35	0-5 in RA (usually leucocytosis)	
			40-70 in SLE	14, 43, 57
Differential count	(relative lymphocytosis ¹)	0-20	0-5 in RA 0-5 in SLE (usually lymphopenia)	9, 43, 57
Eosinophilia	(> $350 \times 10^6/l$)	5-40	5-15 in RA 0-10 in SLE	9, 14, 43, 57, 67
Thrombocytosis	(> $450 \times 10^9/l$)	unusual	40-80 in RA	31
Thrombocytopenia ²	(< $150 \times 10^9/l$)	unusual	10-60 in SLE	14, 67
Serological abnormalities				
Elevated ESR		50-100	50-100	9, 14, 43, 57
Elevation of other phase reactants		sometimes	up to 100	14, 43
Hypergammaglobulinaemia (usually IgG and/or IgM)		50-90	50-90	9, 14, 43, 57, 67
M-component		sometimes	sometimes	9, 43, 57, 67
Immune complexes		approx. 85	50-? in SLE normal or increased in active RA	36
Complement level		normal or increased	(normal or) decreased in active SLE	14, 57, 67
Cryoglobulins		sometimes	sometimes	14, 43, 67
Elevated s-amylase		10-30	0-20	67
Low s-bicarbonate (renal tubular acidosis)	(< 21.3 mmol/l)	10-20	unusual, only in SLE	57
Elevated s-creatinine	(> 0.13 mmol/l)	5-20	20-70	14, 43, 57
Proteinuria	(> 0.2 g/24h)	5-25	30-50	14, 43, 57
Elevated s-beta-2-microglobulin		30-50	30-50	45, 60

¹ For number of B- and T-lymphocytes and the relative proportion of subtypes of T-lymphocytes – see section on Immune regulation p. 147.

² Spontaneous platelet aggregation due to immune complexes may cause a false low thrombocytopenia – called pseudothrombocytopenia (42).

cytes has shown that certain HLA alloantigens may be markers for certain inflammatory connective tissue diseases. Thus, in about 50% of cases, classical/definite rheumatoid arthritis is associated with HLA-Dw4, a frequency which is increased to 85% in rheumatoid arthritis patients with secondary SS (41) (Table 2). It is an interesting fact that the frequency of HLA-Dw2 is significantly decreased in the same group of patients (Table 2). In contrast, patients with primary SS have a significantly increased (approx.

60%) frequency of HLA-Dw2 and/or -Dw3 while at the same time -Dw4 is significantly underrepresented (41) (Table 2). In the same series of patients with primary SS the frequency of HLA-B8 was significantly raised. These findings partly support earlier alloantigen examinations in SS patients (11, 22, 27) and also support the classification of SS patients into a primary and a secondary form.

Other B-lymphocyte antigens (Ia), different from those controlled by the D-locus, have been

Table 2
HLA antigens in primary and secondary Sjögren's syndrome

Antigens	Primary Sjögren's syndrome (per cent)	RR	Secondary Sjögren's syndrome (per cent)	RR	Controls (per cent)	References
HLA-Dw2	approx. 60	3.7	approx. 8 in RA approx. 57 in SLE*	0.24 3.7	26	41, 54
HLA-Dw3	approx. 50	2.8	normal in RA approx. 46 in SLE*	3.0	26	41, 54
HLA-Dw4	approx. 6	0.28	approx. 85 in RA normal in SLE*	22.8	20	41, 54
HLA-B8	approx. 55	3.6	not increased in RA not increased in SLE*		25	41, 54

RA: rheumatoid arthritis

SLE: systemic lupus erythematosus

RR: relative risk

* In the study cited (54) it is not mentioned whether the patients besides their SLE had secondary Sjögren's syndrome.

identified (54). For the antiserum Ia-715 it is found that the frequency of positive reactions is 68% in primary SS and 9% in patients with secondary SS (48).

Autoantibodies

Autoantibodies (Table 3) frequently occur in patients with SS, systemic lupus erythematosus being the only other disease showing the presence of similar numbers. It is noteworthy that an antibody against liver-cell-membrane (LMA) is found in about 20% of cases with SS since LMA is usually assumed to occur only in patients with HBsAg-negative chronic active inflammatory liver disease (39).

In spite of the existing uncertainty with regard to the organ-specificity of LMA, the demonstration of LMA in sera from patients with Sjögren's syndrome may suggest inflammatory liver involvement in patients with primary or secondary Sjögren's syndrome.

Information on the frequency of antibodies to the different extractable nuclear antigens in primary Sjögren's syndrome, and in secondary Sjögren's syndrome with its closely associated diseases, has recently become available as va-

rious purified nuclear antigens have been isolated.

In 1977, Akizuki et al. (1) succeeded in purifying an acidic nuclear antigen from calf thymus with a molecular weight of 43,000. The antigen – called Ha – lacks tyrosine or histidine residues as demonstrated by failure of iodination by chloramine-T or lactoperoxidase. Anti-Ha autoantibodies have been shown to be immunologically identical with anti-SS-B antibodies (2) and are probably similar to anti-SjT autoantibodies (3). These autoantibodies are seen in 70–80% of patients with primary Sjögren's syndrome (2, 33), whereas the frequencies in patients with rheumatoid arthritis and Sjögren's syndrome and in controls were below 10% (2, 33). Recently, another acidic nuclear antigen with a molecular weight of 68,000 has been purified (65). Serum antibodies against this antigen are typically found in patients with primary Sjögren's syndrome, and less commonly in patients with rheumatoid arthritis and systemic lupus erythematosus (65). However, the occurrence of these antibodies in patients who strictly fulfil the definition criteria and are HLA-Dw2 and/or HLA-Dw3 positive, is not known. It is relevant to hypothesize that the autoantibodies against Ha,

Table 3

Prevalence of different autoantibodies (ab) in primary and secondary Sjögren's syndrome

Autoantibody	Primary Sjögren's syndrome (per cent)	Secondary Sjögren's syndrome (per cent)	References
ANA (Anti-nuclear ab)	60-90	up to 100	9, 39, 57
C3F-ANA (Complement C3-fixing ANA)	60-80	60-80	39
GS-ANA (Granulocyte specific ANA)	0-10	40-60 in RA 10-15 in SLE	39
C3F-GS-ANA (Complement C3-fixing GS-ANA)	0- 5	30-50 in RA 0- 5 in SLE	39
Anti-SS-A, -B and/or anti-Ha ab	50-80	0-15 in RA 60-90 in SLE	1, 2, 33, 48
RAP (Rheumatoid arthritis prec.)	5-15	70-90 in RA 0- 5 in SLE	2
Anti-DNA ab	0-(5)	0-(5) in active RA (95)-100 in active SLE	39
Anti-RNP ab (Ribonucleoprotein)	not known	0-10 in RA 25-35 in SLE	43
Anti-Sm ab (Smith)	not known	0-(5) in RA 25-35 in SLE	43
Waalser-Rose	30-60	60-95 in RA	39, 43, 57
RAT (Rheumatoid arthritis test)	40-80	60-90 in RA	39, 57
Positive Coombs' test	0-15	5-20	9, 14, 57, 67
Positive LE-cell phenomenon	0-20	20-40 in RA 80-100 in SLE	9, 14, 43, 57
Positive WR	0- 5	5-30 in SLE	9, 14, 43
Platelet ab	not known	60-80 in SLE	14, 43
Lymphocyte ab	not known	60-80 in SLE	14, 43
SGA (Salivary gland ab)	30-60	10-40	39, 57, 67
Pancreatic duct cell ab	20-40	20-40 in RA	67
SMA (Smooth muscle cell ab)	20-40	20-40	39
AMA (Anti-mitochondrial ab)	0-15	10-30	39
LMA (Liver-cell-membrane ab)	5-25	20-40	39
SKA (Skeletal muscle ab)	0-10	5-20	39
Thyroid ab (microsomal)	10-20	10-20 in SLE	14, 57
PCA (Parietal cell ab)	not increased	not increased	39, 57
Adrenal, pituitary, parathyroid and ovarian ab	not increased	not increased	67

SS-B and KD 68 mainly occur in patients with primary Sjögren's syndrome and less often in patients with secondary Sjögren's syndrome.

Little is known about the association of autoantibody titres with clinical disease activity and paraclinical activity parameters. It has been suggested that the presence of the anti-Ha antibody may identify a subpopulation of SS patients with a greater risk of rapid progression of the disease and/or the development of pseudolymphoma (33).

The amino acid sequences of the antigens Ha, SS-B and KD 68 are not available. Thus the similarities/differences between the antigen(s) remain to be solved.

ATOPY – DRUG ALLERGY

Besides the increased frequency of eosinophilia it has been reported that patients suffering from Sjögren's syndrome may be more often allergic to penicillin (9) than others – a finding also seen in our series of primary SS patients, the frequency being 17%. Side effects from goldsalts and penicillamine in patients with primary SS have not been reported from among extensive series. In our primary SS patients toxicity or hypersensitivity to goldsalts were seen in 75% of cases ever treated with goldsalts and in three of three patients treated with penicillamine. These figures are in accordance with those reported by Wooley et al. (68) who found side effects in 81% of rheumatoid arthritis cases treated with gold-salt – but it is important to note that the reaction to goldsalt occurred among patients who had HLA-Dw2 and/or -Dw3 (68): the antigens seen in primary SS patients. Further data are needed to verify whether side effects to goldsalts and/or penicillamine are seen especially among SS patients and perhaps primarily in those with HLA-Dw2 and/or HLA-Dw3.

Balint et al. (6) reported evidence of an increased risk of side effects during treatment with levamisole in patients with rheumatoid arthritis and secondary Sjögren's syndrome.

IMMUNOREGULATION

The presence of polyclonal hypergammaglobu-

linaemia, the several organ-specific and non-organ-specific antibodies, as well as circulating immune complexes (Tables 1 and 3), all suggest a polyclonal B-lymphocyte hyperreactivity as also seen in systemic lupus erythematosus. However, in contrast to systemic lupus erythematosus, where a highly increased number of active circulating B-lymphocytes are found, patients with primary SS seem to have normal concentration of B-lymphocytes in the peripheral blood (49). Whether or not activated B-cells may be found in increased numbers in the lymphoid organs of patients with primary SS remains to be solved.

Our knowledge of the background for the pronounced B-lymphocyte hyperreactivity in primary SS is sparse. The total number of peripheral T-lymphocytes is normal; in contrast to the low level in systemic lupus erythematosus. When analysing the relative proportions of subtypes of T-cells, Moutsopoulos & Fauci (49) found that the number of T_s-cells (or suppressor T-cells) was significantly reduced in peripheral blood in patients with extraglandular primary SS whereas normal concentration of T_s-cells was usually seen in patients with "only" glandular involvement (49). In the same study it was shown that the low amount of T_s-cells was probably due to a trypsin-sensitive serum factor that blocked the Fc-receptor of the T_s-cells. Trypsinization of the T-cells before analysing for the Fc-receptor could increase the low T_s-cell concentration to the normal range. Other *in vitro* experiments showed that the serum factor from patients with primary extraglandular SS could lower the T_s-cell number in normal controls (49).

At present it may be concluded that concentrations of B- and T-lymphocytes – in peripheral blood of patients with primary SS – are within normal limits. However, the B-lymphocytes seem to be hyperreactive and this activity is possibly also manifest in lymphoid tissues outside the blood circulation. The distribution of the different lymphocyte classes and their activity in tissues – especially in SS patients with pseudolymphoma – is not known, but exploration is certainly needed.

IMMUNOGLOBULINS AND OTHER PROTEINS IN SALIVA AND TEAR FLUID

Analyses of the composition of tear fluid and saliva in SS may throw light on some basic pathophysiological abnormalities. Immunochemical studies on normal saliva and tear fluid have shown that – as in other secretions – IgA is the dominating immunoglobulin.

Secretory and also salivary IgA has a sedimentation coefficient of 11S. The 11S IgA consists of IgA dimers bound to secretory protein (SP) through disulphide- and non-covalent bonds. SP serves to stabilize the immunoglobulin molecule against enzymatic degradation and to facilitate the transportation of IgA from the glandular cells to the secretory ducts.

Several studies of SS patients have dealt with the analysis of immunoglobulins in saliva and with the *in vitro* synthesis of proteins by lymphoid cells obtained by labial biopsy. Local synthesis of the immunoglobulins IgM and IgG in large quantities, as well as the presence of IgG rheumatoid factor in salivary glandular tissue, strongly suggest B-lymphocyte hyperreactivity (4). Investigation of saliva by radioimmunoassay has shown that rheumatoid factor of IgA and IgM classes occurs in patients with primary or secondary SS (15). It is unknown at present why the lymphocytes accumulate in the salivary glands, to what extent the lymphocytes contribute to the tissue damage and to the synthesis and secretion of the different rheumatoid factors. It is noticeable that treatment of SS with either cyclophosphamide or bromhexine may reduce one or more of the immunoglobulins in saliva if they are present in large amounts (4, 40, 50).

Other proteins like the β_2 -microglobulin (45) and the vitamin B₁₂-binding protein, so-called R-binder, appear in higher concentration in saliva in primary and secondary SS patients than in normal individuals. Furthermore, the concentration of salivary β_2 -microglobulin may permit estimation of the lymphocytic inflammation in the salivary glands (45).

Normal tear fluid contains amounts of secretory IgA and IgG. The other Ig-classes can only be detected in variable amount. At the present

time, studies of Ig content in the tear fluid from patients suffering from SS, are not known to the authors.

Studies of other eye diseases in which an immunopathological mechanism may be suspected have shown that secretory IgA levels are normal or reduced, while IgG concentrations are high in cases with corneal ulcer (10) and reduced in cases with trachoma (44, 56). The concentrations of the complement factors C₃ and C₄ have been found to deviate in the patients with corneal ulcer and trachoma (10) compared with healthy persons (69).

The method of lysozyme determination and its values in Sjögren's syndrome have been described (p. 141).

An *in vitro* blastogenic response of patient lymphocytes to corneal stroma has recently been reported (18). These observations suggest lymphocyte-mediated organ-specific autoimmunity in SS.

IMMUNECOMPLEXES AND THE RETICULOENDOTHELIAL SYSTEM

Only a single report (36) describes the circulating immune complexes (CIC) in primary and secondary SS. Using a ¹²⁵I-C1q binding technique Lawley et al. (36) found that 85% of the patients with SS had CIC independently of primary, secondary and clinical activity subcategories. This is in contrast to the findings in systemic lupus erythematosus (19). Using pretreatment with 10⁻² M 2-mercaptoethanol as well as protein A absorption experiments it was convincingly demonstrated that ¹²⁵I-C1q was practically always bound to IgG in the CIC and only minimally to 19S IgM rheumatoid factor, which are often present in SS sera (36).

Clearance of the CIC is supposed to occur mainly in the reticuloendothelial system represented by phagocytic mononuclear cells that have Fc-receptors on their cell surface. The *in vivo* function of these Fc-receptors can be evaluated by injecting IgG-sensitized radio-labelled (⁵¹Cr) autologous erythrocytes and assuming that the erythrocyte clearance follows a similar clearing procedure as that of the CIC. Using this model it was found that the Fc-re-

ceptor function was often disturbed in primary SS, as indicated by decreased clearance of the coated erythrocytes (26). The abnormal Fc-receptor function was highly correlated to extra-glandular SS manifestations. Normal Fc-receptor function was found in SS patients with glandular disease activity only (26). These findings partly resemble those found in systemic lupus erythematosus, where the Fc-receptor function is decreased in cases with active disease while it is normal in silent cases.

CELLULAR HYPERSENSITIVITY

Disturbances of lymphocyte-mediated immunity is another important feature of SS. Phyto-haemagglutinin stimulation *in vitro* of peripheral lymphocytes from SS patients gives a lower response than in normals (38). On the other hand, it has been shown that T-lymphocytes from patients with primary SS gave a normal stimulatory response to concanavalin-A and pokeweed-mitogen, in contrast to the low values seen in patients with active systemic lupus erythematosus (48).

Impaired delayed cutaneous hypersensitivity to the specific antigens tuberculin and dinitrochlorobenzene suggest that the cellular immune mechanisms are involved (38). The phenomenon, however, is more pronounced in patients with rheumatoid arthritis and secondary Sjögren's syndrome than in patients with primary Sjögren's syndrome (38). Organspecific inhibition of leucocyte migration *in vitro* confirms that cell-mediated autoimmunity is another feature of SS (61).

It is noticeable that SS has been described in several patients treated for haematological disorders with bone-marrow transplants (24). The recipients developed symptoms of keratoconjunctivitis sicca and xerostomia about a year after transplantation and showed lymphocytic infiltration in the lip biopsy even though the donors had compatibility at the HLA-A and B loci and showed no reactivity in mixed lymphocyte cultures. The severity of the symptoms corresponded with the severity of the histological lesions, but none of the patients had rheumatoid factor, or other antibodies in serum (24).

Recognition of host antigens in the target organ by donor lymphocytes may probably give rise to a graft-versus-graft host disease resembling SS (24).

AETIOLOGY AND PATHOGENESIS

As with the other chronic inflammatory connective tissue diseases, little is known about the aetiological factors in primary SS. Based on the studies showing HLA and Ia association it is evident that genetic factors are of importance. The influence of environmental factors is unknown and to the best of the authors' knowledge description of primary SS in monozygotic twins has not been reported. Bacterial or viral infections have not been found consistently associated with primary SS.

The consistent presence of several autoantibodies in high titres and the often pronounced hypergammaglobulinaemia suggest that several types of immune complexes might occur – either in peripheral blood or in the other tissues. The deficient Fc-receptor function in some primary SS patients could predispose to increased survival and tissue deposition of circulating immune complexes with damage and inflammatory reactions to follow. It is not known whether some types of circulating immune complexes in primary SS are more damaging for the different tissues than others. However, it must be remembered that the life-span of the SS patients without lymphoproliferative disease seems equal to that of the general population. This points to the hypothesis that the various circulating immune complexes are less damaging than those associated with systemic lupus erythematosus.

Since modern techniques for measuring the different autoantibodies and immune complexes as well as the various subgroups of lymphocytes are rapidly improving, it is possible to predict the kind of protein(s) and/or cell(s) that will be shown to fluctuate and correlate best with disease activity. The results available at present do not seem to indicate factor(s) that are changing their activity or function as a new disease stage develops – as e.g. anti-DNA antibody in systemic lupus erythematosus with development of renal insufficiency. This indicates that

the pathophysiological mechanisms involved in primary SS are less severe than those involved in the pathogenesis of systemic lupus erythematosus.

DIFFERENTIAL DIAGNOSIS

The disease that most often resembles primary Sjögren's syndrome is systemic lupus erythematosus. Both diseases have usually a multi-organ involvement and several different autoantibodies are present. Clinically, primary SS and systemic lupus erythematosus can be distinguished if the salivary (or lacrimal) glands are repeatedly swollen and hard, as these signs are seldom seen in systemic lupus erythematosus. Severe CNS involvement and compromised renal function with elevated S-creatinine and abnormal glomeruli is most typically seen in systemic lupus erythematosus.

The laboratory test which we at present consider the best one to distinguish between primary SS and systemic lupus erythematosus is anti-DNA ab. determination. In active stages of disease only systemic lupus erythematosus will provoke clearly elevated values – this will not be the case in primary SS. At present it is not definitely known if determination of so-called anti-SS antibody will be of value. It is our hypothesis that anti-SS antibodies may be highly specific for primary SS.

It is of prognostic importance to know whether the patient has primary SS or systemic lupus erythematosus. Although the disposition to lymphoid neoplasia is increased to about the same level in both categories, the serious involvement of the kidney, heart and CNS is mainly seen in systemic lupus erythematosus and will often require different management and treatment.

Rheumatoid arthritis can be differentiated from primary SS by the presence of erosions and destructions on X-ray of the hands or feet, as these changes do not seem to develop (or only slightly) in primary SS. Patients are usually pleased when they learn that their disease has nothing to do with rheumatoid arthritis and that they will not develop the end stages in hands and feet, which they usually know is the prob-

able fate of rheumatoid arthritis patients.

Tissue typing of the -D region may be of value in cases of doubt, as the presence of HLA-Dw4 strongly suggests rheumatoid arthritis and speaks against primary SS. On the other hand, HLA-Dw2 and/or -Dw3 strongly suggest primary SS and – especially -Dw2 – speak against rheumatoid arthritis. It is still not established whether patients with HLA-Dw3 and -Dw4 are those who start with a multiple organ involvement and later develop the erosions and destructions seen on X-ray. The combination of HLA-Dw2 and HLA-Dw4 seems to be extremely rare.

From a therapeutic point of view it is of the utmost importance to know whether the patient has primary SS or rheumatoid arthritis with secondary SS. It has never been proved in clinical trials that treatment with goldsalts, penicillamine, etc. are of any value in primary SS. On the contrary it seems that the risk of developing side effects from these drugs is very high, and thus should not be used (see section on atopy and drug allergy p. 147). Patients with rheumatoid arthritis and secondary SS do not seem more prone to develop side effects from gold and/or penicillamine than other patients with rheumatoid arthritis.

The differential diagnoses against polymyositis, progressive systemic sclerosis, mixed connective tissue disease and other chronic inflammatory connective tissue diseases are usually simple to make after thorough clinical investigation. In doubtful cases specific antibody determination will settle the question in most cases.

Dryness in the eyes and mouth due to medications, X-ray irradiation, earlier extirpation of glands, diabetes mellitus, etc. are usually excluded by simple methods.

MANAGEMENT AND TREATMENT

Any patient with SS should be seen by an ophthalmologist and a rheumatologist and most patients should be regularly seen by both. The object is primarily to reduce and prevent the development of irreversible ocular damage, and secondly to detect lymphoid neoplasia as early as possible.

LOCAL TREATMENT

For the local treatment of xerostomia frequent intake of non-acidic fluids; sugar-free chewing gum; spraying with polyvinylalcohol, etc. may be prescribed.

For the local treatment of keratoconjunctivitis sicca mucomimetics such as methylcellulose and polyvinylalcohol are the eye drops most commonly used and both medicaments reduce the symptoms. Other medicaments and types of treatment have been discussed (21).

SYSTEMIC TREATMENT

Treatment with corticosteroids has proved beneficial in cases of severe and active primary SS, and immunosuppressive agents (cyclophosphamide and azathioprine) have also been tried. However, randomised controlled trials are not available. Further, both types of treatment entail a risk of serious side effects that appears to be out of proportion to the chronic, and usually benign course, of primary SS.

Treatment with goldsalts and/or penicillamine are contraindicated, partly due to the number of side effects that may be expected to occur in primary SS, and partly because of its never proven capacity to stop the disease processes in primary SS.

The need for symptomatic treatment of the various disease manifestations in primary SS depends on their severity. Acetylsalicylic acid or other non-steroid antiinflammatory drugs may be necessary for the arthralgia; phentolamine or prazosine can be tried in severe Raynaud cases, etc.

Some experience has been gained in recent years in the treatment of SS with bromhexine (Bisolvon®). Bromhexine has been used in Western Europe for the treatment of chronic bronchitis for the past decade. It has been shown to increase the quantity of bronchial secretion and to reduce viscosity. The drug is derived from a herb that has been used in Indian folk medicine for centuries, but its mechanism of action is unknown. No serious side effects have been reported.

Complete remission of symptoms from SS was observed in one patient with severe eye symptoms (32), and on this background two randomised clinical trials have been carried out (20, 40). The results suggest a dose-related effect of bromhexine on lacrimal secretion in patients with SS. The values for break-up time and Schirmer tests (20, 40) as well as the corneal sensitivity (40) all increased significantly during treatment with bromhexine. Also a decrease in salivary IgM concentration was observed (40). This supports data from open studies, where it has been shown that the concentration of salivary IgA and IgG may fall following bromhexine (50) – possibly due to an increased volume of saliva. In a few of our patients, relief of severe xeroderma and vaginitis sicca symptoms occurred during bromhexine treatment.

At present, bromhexine (24–48 mg/day given orally, divided into three doses) is our first choice in the systemic treatment of SS.

An interesting aspect of bromhexine treatment for Sjögren's syndrome is that research into its mechanism of effect might provide further information regarding the aetiology and pathophysiology of Sjögren's syndrome.

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Address:

R. Manthorpe, M.D.
 Medical Department TA 7551
 State University Hospital
 Tagensvej 20
 DK-2200 Copenhagen N
 Denmark

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