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Research Article

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The salivary gland lymphocytic infiltrates present in labial biopsy specimens were compared in 10 patients using an indirect immunofluorescent method with anti-human T cell serum and a quantitative focus-scoring method. In general, there was a correlation between the number of T cells and the extent of the infiltrate. Striking accumulations of T cells were present in some patients, but clusters of presumed B cells were also seen. These results indicate an increase in peripheral blood B cells in most patients, a decrease in T cells in some, and a mixed T and B cell infiltrate in the salivary gland lesions.

T and B Lymphocytes in Peripheral Blood and Tissue Lesions in Sjögren's Syndrome

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ABSTRACT Lymphocyte heterogeneity was studied in peripheral blood and salivary gland lesions in 24 patients with Sjögren's syndrome. Peripheral blood B cells, measured by immunofluorescence with specific antiserum to immunoglobulins or by rosette assay with complement-coated erythrocytes, were increased in most patients. Peripheral blood T cells, measured by immunofluorescence with rabbit antiserum to human thymocytes or by rosette assay with sheep erythrocytes, were reduced in eight patients. Three had associated rheumatoid arthritis, two had a generalized lymphoproliferative disorder, and one each had scleroderma, systemic lupus erythematosus, and neuropathy.

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INTRODUCTION

Sjögren's syndrome (SS) is a chronic inflammatory disorder in which salivary and lacrimal glands become heavily infiltrated by lymphocytes leading to decreased production of saliva and tears (1, 2). A connective tissue disease, most often rheumatoid arthritis, is present in the majority of patients. Some subjects develop a generalized lymphoproliferative disease which can take a variety of clinical forms, including Waldenström's macroglobulinemia, pseudolymphoma, and a highly malignant reticulum cell sarcoma (3–5). It is noteworthy that the only monoclonal gammopathy observed in SS has involved the IgM immunoglobulin class in every instance (5).

Rheumatoid factor, anti-nuclear factor, and anti-salivary duct antibody are commonly present in the serum along with hypergammaglobulinemia. The minor salivary glands of the lower lip are infiltrated with lymphocytes and offer a readily accessible area to biopsy for histologic confirmation of the diagnosis and for immunologic investigation (6–8). In a patient with coexisting SS and Waldenström's macroglobulinemia, the monoclonal IgM was produced by lymphoid cells in the labial biopsy (7).

Recent attention has focused on understanding the precise role of lymphocytes in many human disorders. Lymphocytes themselves have been divided into two basic groups: (*a*) B cells, derived from bone marrow, readily identified by surface immunoglobulins (Ig) and predestined to serve in the production of humoral antibody (9–15), and (*b*) T cells, derived from thymus, possessing no readily demonstrable surface Ig but characterized by another antigenic marker (theta), and predetermined to carry out the functions of cellular immunity (16–19).

It is not yet clear how actual tissue lesions are produced in diseases such as systemic lupus erythematosus, rheumatoid arthritis, or SS, but many investigators have emphasized the predominance of lymphocytes demonstrable in the tissue lesions themselves (20, 21). In rheumatoid arthritis and SS, large amounts of immunoglobulins and rheumatoid factor are produced in these

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tissues lesions, suggesting the presence of B cells (7, 8, 20, 23). Whether B cells are the predominant lymphocyte population present, or whether there are varying numbers of B and T cells in different patients, is not known. The availability of labial biopsy material from patients with SS and of several new methods to identify T and B cells have enabled us to study this question and to assess the role of various populations of peripheral blood lymphocytes in this disease complex.

METHODS

Patients. 24 patients (19 female, 5 male) ranging in age from 24 to 76 yr were evaluated as outpatients in the Sjögren's Syndrome Clinic established at the University of California, San Francisco. The evaluation included measurement of stimulated salivary flow from both parotid glands, labial gland biopsy (6), determination of salivary gland function by scintigraphy using sodium pertechnetate Tc99m (24), and careful ophthalmologic study including Schirmer test, rose bengal staining, tear lysozyme measurement, and slit lamp examination. Routine immunologic studies included measurement of serum immunoglobulins by radial immunodiffusion and determination of antinuclear factor, rheumatoid factor, and anti-salivary duct (25) antibody.

Lymphocyte studies. Lymphocytes were isolated from peripheral blood drawn into heparinized syringes by differential centrifugation through Ficoll-Hypaque (26, 27). In some instances cells were studied on two separate occasions; single determinations were performed in most patients. B cells were identified by two methods. In the first, direct immunofluorescence was performed using immunoabsorbent purified antibodies to IgG, IgA, and IgM as previously described (9–12, 27, 28). The total number of B cells was determined by adding percentages of cells staining for surface IgA+IgG+IgM since previous studies in our laboratory and by other (28–30) have indicated that normal lymphocytes usually contain one major class of Ig on the surface of an individual cell. Some peripheral blood lymphocyte preparations obtained after Ficoll-Hypaque separation contained 5–10% monocytes; however with experience these could be identified using simultaneous phase microscopy or in some instances by adding small latex beads (27). In all cases cell viability as measured by trypan-blue dye exclusion was 95% or greater. In the second method, B cells bearing the C'3 receptor were identified by rosette formation with sheep erythrocytes coated with human complement (31).

T cells were identified using two parallel methods. In one, cells were examined by direct immunofluorescence using rabbit antiserum against human fetal thymocytes prepared as previously described (28) and absorbed with large numbers of B cells obtained from patients with chronic lymphatic leukemia. Normal values for T cells using this method in over 100 normal subjects to date are 79.5±16.2%. The second method used for identification of T cells was the E-binding rosette method as described by several groups (15, 32–35). Normal values for T cells using this method in 62 normal subjects were 64.3±13.7%. Great care was taken to standardize this assay and results were reproducible from day to day using a group of normal subjects tested over a several months period. It was found that good reproducibility could be obtained particularly if a strict regimen of technique was adhered to as described by Ross, Rabellino, Polley, and Grey (15) and if fresh sheep erythrocytes no older than 7–8 days were used.

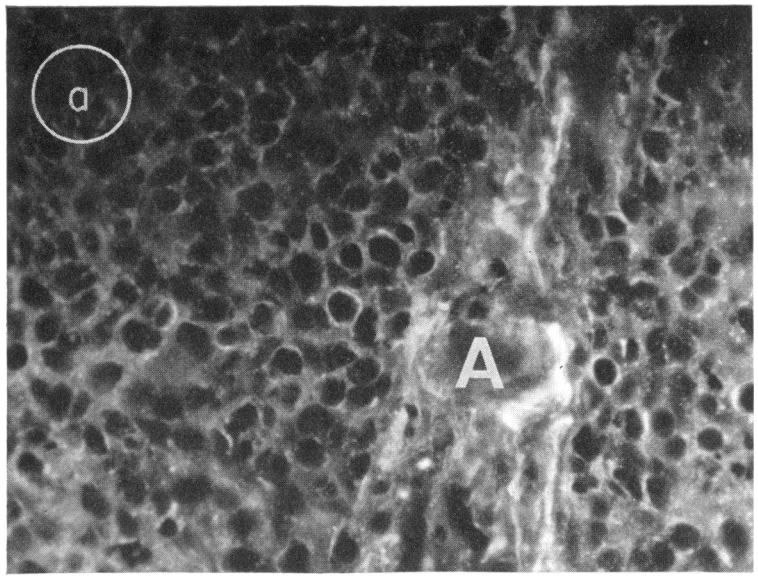
Immunofluorescent studies of tissues. Labial biopsy specimens were cryostat-sectioned, kept cold, and examined using indirect immunofluorescence with rabbit anti-human thymocyte antiserum and conjugated goat anti-rabbit IgG. The latter was employed in a dilution of 1:2 and 1:4 to ascertain the relative proportions of lymphocytes within the salivary gland lesions themselves identifiable as T cells. The goat anti-rabbit IgG antiserum was previously absorbed using human IgG made insoluble on immunoabsorbent column to avoid any cross-reaction with human IgG in tissues. 200–300 cells were counted and proportions of tissue lymphocytes identified as thymus-derived were estimated by immunofluorescence. Staining of frozen sections of human thymus showed rim or membrane staining of 95–97% of thymic lymphocytes. In addition staining of fresh frozen sections of adult human spleen showed predominance of staining of periarteriolar (thymus-dependent) regions; however some faint follicular staining apart from splenic periarteriolar regions was also noted. Examples of such staining patterns of normal human spleen sections are shown in Fig. 1.

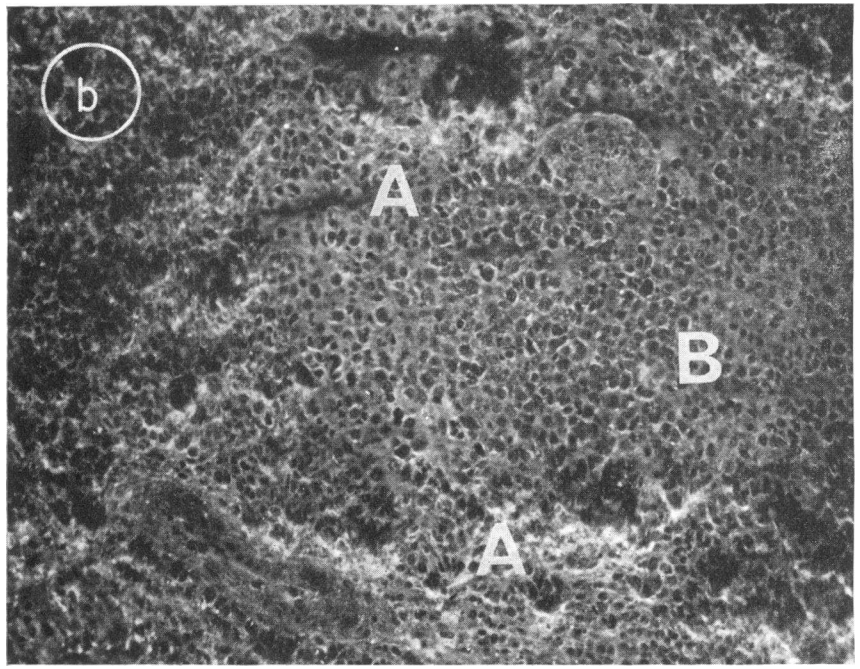
Relative infiltration of lip biopsy material by T cells identified by fluorescent techniques was compared with conventional histologic grading using a focus scoring method whereby individual foci are enumerated. The focus score is defined as the number of foci of 50 or more mononuclear cells in a 4 mm^2 area (6).

RESULTS

Clinical findings. 20 patients were classified as definite SS (Table I) on the basis of a history of dry eyes and mouth, objective evidence of keratoconjunctivitis sicca, a marked degree of lymphocytic infiltration of the labial salivary glands (6), and a diminished parotid salivary flow. 12 of these patients also had a severely abnormal salivary scan (24). Parotid swelling was present in three patients, rheumatoid arthritis in five, pseudolymphoma, neuropathy, systemic lupus erythematosus, macroglobulinemia, and sclerodema in one each, respectively. One patient with rheumatoid arthritis also had extensive lymphocytic infiltration of the lung.

Four patients were classified as possible SS on the basis of a suggestive history and some supporting laboratory evidence (Table I). As used in our clinic, the diagnosis of SS in the absence of an underlying connective tissue disease requires objective evidence of both lacrimal and salivary gland involvement. Three of the patients had either insufficient or equivocal evidence of keratoconjunctivitis sicca even though one (A. A.) had an abnormal number of lymphocytes present in the labial biopsy. The fourth was a young man with severe keratoconjunctivitis and decreased salivary flow whose labial biopsy and salivary scan were normal. Although by less stringent criteria some of these patients might qualify as having SS, their disease is sufficiently early, mild, or atypical to merit consideration as a separate group.





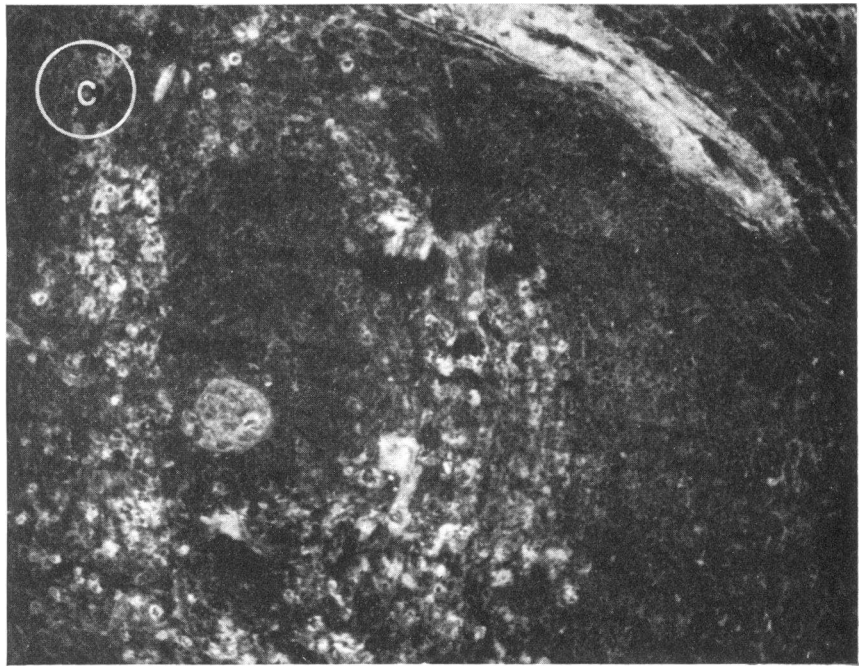


FIGURE 1 (*a*) Representative indirect rabbit anti-human thymus antiserum immunofluorescent staining patterns of normal human spleen are shown. Particularly strong cell membrane staining in cells surrounding the arteriole marked *A* is noted whereas the cells more distant from the arteriole as in the upper left corner show slightly diminished staining reactions. (Magnification × 600) (*b*) Immunofluorescent photomicrograph of lymphoid follicle in normal human spleen stained by indirect immunofluorescence and rabbit antihuman fetal thymocyte antiserum. The peripheral portions of the follicle marked *A* which are also near small arterioles show considerably more fluorescence using this reagent than the middle portion of the follicle marked *B*. There was, however, faint membrane fluorescence of some central lymphoid cells. (Magnification × 350) (*c*) Direct immunofluorescent staining for IgG of same general human splenic area as shown in Fig. 1*b*. Cells staining for cytoplasmic IgG show a central and more diffuse distribution than is noted with the anti-T-cell reagent and indirect immunofluorescence in 1*b*.

Serum immunoglobulins and B cells. Serum immunoglobulin concentrations and the percent of B lymphocytes of each class are presented in Table II. Of the 20 patients with definite SS, 14 have abnormal elevations of IgG ($\geq$ 1,500 mg/100 ml), 6 of IgA ($\geq$ 400 mg/100 ml), and 12 of IgM ($\geq$ 115 mg/100 ml). With regard to B cells, 9 have elevated percentage of IgG-bearing cells ($\geq$ 12%), 6 of IgA-bearing cells ($\geq$ 6%), and 12 of IgM-bearing cells ($\geq$ 12%). No clear correlation was noted between the serum immunoglobulin concentration and the percent of B cells belonging to a given Ig class.

One patient (E. P.) had associated Waldenström's macroglobulinemia and was producing a kappa-type IgM paraprotein. Her bone marrow showed no increase in lymphocytes and peripheral blood did not contain an abnormal number of IgM-bearing cells as tested both by immunofluorescence and by cytotoxicity.

The results in the patients with possible SS are largely within normal range except for C. H. (Table II). This unusual patient whose clinical findings were already discussed (Table I) had an increased serum IgG and an increased percent of IgM-bearing lymphocytes.

The general increase in B cells is shown most graphically in Table III where the sum of IgG + IgA + IgM cells is indicated. Many patients also had an increase in cells with receptors for C'3 as indicated by rosette formation with complement-coated erythrocytes (EAC).

T cells in peripheral blood. The percent T cells detected by immunofluorescence or by rosette formation with sheep erythrocytes was normal in the majority of

TABLE I
Clinical and Diagnostic Features

Patient	Age Sex	Keratoconjunctivitis sicca (KCS)	Labial biopsy grade	Salivary flow	Salivary scan class	Remarks
	yr			*ml*		
Definite Sjögren's syndrome						
E. M.	50 F	Yes	4	0	3	Pseudolymphoma
E. K.	74 F	Yes	4	0	4	Parotid swelling
M. D.	74 F	Yes	4	0	4	
G. S.	60 F	Yes	4	0	3	Neuropathy
D. McG.	53 F	Yes	4	0	4	Scleroderma
E. L.	46 F	Yes	4	0	4	
M. H.	59 F	Yes	4	2.1	1–2	
S. G.	24 F	Yes	4	3.4	—	
B. J.	30 F	Yes	4	0.8	4	Parotid swelling
F. Wi.	44 F	Yes	4	0	4	SLE
L. McE.	60 F	Yes	4	0.3	4	
G. L.	49 F	Yes	4	4	1	
F. We.	53 M	Yes	4	3.5	1	Rheumatoid arthritis
E. McD.	48 F	Yes	4	6	1	
R. W.	54 M	Yes	4	4	2	Rheumatoid arthritis and rheumatoid lung
J. H.	76 M	Yes	4	4	—	Rheumatoid arthritis
E. P.	69 F	Yes	4	0	4	Macroglobulinemia
D. T.	61 F	Yes	4	0	4	Parotid swelling
M. N.	56 F	Yes	4	0.5	4	Rheumatoid arthritis
H. C.	66 M	Yes	4	8.3	1	Rheumatoid arthritis
Possible Sjögren's syndrome						
C. H.	25 M	Yes	2	1.6	2	
A. P.	69 F	No	2	0.8	2	
B. C.	45 F	No	2	5.3	2	Rheumatoid arthritis
A. A.	40 F	?	4	1.3	1	Raynaud's phenomenon

The diagnosis of keratoconjunctivitis sicca was made on the basis of Schirmer test, rose bengal staining, tear lysozyme measurement, and slit lamp examination. The degree of lymphocytic infiltration of the labial salivary glands was graded 0–4 using the criteria of Chisholm and Mason (6) in which four (more than one focus per 4 mm^2) is consistent with Sjogren's syndrome. The stimulated parotid saliva was collected and measured by a technique in which normal values exceed 6 ml/10 min per gland. The salivary scintigraphic scans were classified as previously described (24) in which class 1 is normal, class 2 is mild to moderate involvement, and classes 3 and 4 represent severe involvement.

TABLE II

Serum Immunoglobulins and Ig-Bearing Lymphocytes

Patient	Serum			Lymphocytes		
	IgG	IgA	IgM	IgG	IgA	IgM
	mg/100 ml			%	%	%
Definite Sjögren's syndrome						
E. M.	3,900	330	270	12	3	18
E. K.	3,500	215	95	21	3	9
M. D.	3,300	420	34	18	2	4
G. S.	2,750	195	66	11	1	9
D. McG.	2,600	400	242	17	7	18
E. L.	2,150	1,000	115	9	3	10
M. H.	2,000	0	95	18	2	19
S. G.	1,800	640	170	9	1	13
B. J.	1,750	140	270	10	3	10
F. Wi.	1,650	400	730	15	2	19
L. McE.	1,650	660	51	17	6	14
G. L.	1,650	260	115	16	12	6
F. We.	1,500	205	82	24	7	13
E. McD.	1,500	140	82	12	2	12
R. W.	1,400	280	310	13	4	14
J. H.	1,300	390	65	12	4	13
E. P.	1,100	290	1,250*	9	6	7
D. T.	1,000	260	600	12	4	14
M. N.	940	340	195	39	13	25
H. C.	940	380	133	17	3	7
Possible Sjögren's syndrome						
C. H.	1,650	0	115	10	2	15
A. P.	1,200	330	96	12	4	11
B. C.	1,000	225	115	15	1	11
A. A.	940	380	51	7	0	11
Normal values (±SD)	1,200±320	290±120	80±30	11.7±4.3	3.3±2.6	6.6±2.8

* Paraprotein.

patients (Table III). Seven patients had T cells below 63% by the fluorescent method. Three of these patients (F. We., M. N., H. C.) had associated rheumatoid arthritis while one each had associated scleroderma (D. McG.), systemic lupus erythematosus (F. Wi.), pseudolymphoma (E. M.), and macroglobulinemia (E. P.). Of these seven, three (two with rheumatoid arthritis, one with macroglobulinemia) also had a reduced number of T rosette-forming cells (±50%). One patient with neuropathy (G. S) had 43% T cells by rosette assay but 80% by immunofluorescence.

Assay for lymphocytotoxic and lymphocyte cytophilic antibodies. Since previous studies (36) found lymphocytotoxic antibodies with apparent specificity for T cells in many patients with lupus, all Sjögren's sera were assayed for such antibodies using a panel of lymphocytes from 10 normal donors of widely differing Hl-A haplotypes. Only five patients had lymphocytotoxic antibodies reacting with more than half of the normal test panel. There was no direct correlation between the percentages of peripheral blood T cells and such lymphocytotoxic antibodies.

An attempt was made to see if the relatively high proportions of cells classified as B cells on the basis of cell surface immunoglobulins might be due to surface or membrane adsorption of cytophilic antibody onto lymphocyte surfaces. Accordingly, a series of normal peripheral blood lymphocytes were incubated in undiluted patients' serum for 30 min at 37°C, followed by washing and then staining with fluorescein-conjugated rabbit anti-human IgG. The cells were also examined for surface IgG without preincubation in patients' serum. In three instances Sjögren's sera preincubated with normal test lymphocytes appeared to significantly increase the percentages of cells staining for surface IgG. In these instances cells showing spotty or discontinuous fluorescent surface IgG staining were doubled. 12 normal sera in-

TABLE III

Total Lymphocytes, B cells, and Rosette-Forming Cells

Patient	Total lymphocytes	% Total B cells*	% T cells (RAHT)*	Total B+T	Rosettes	
					E(T)	EAC(B)
Definite Sjögren's syndrome						
E. M.	2,688	33 (887)	52 (1,397)	85	61	9
E. K.	3,060	33 (1,009)	70 (2,142)	103	81	18
M. D.	1,560	24 (374)	78 (1,216)	102	67	17
G. S.	855	21 (179)	80 (684)	101	43	32
D. McG.	1,750	42 (735)	57 (997)	99	75	39
E. L.	1,032	22 (227)	81 (835)	103	70	19
M. H.	1,200	39 (468)	76 (912)	115	74	27
S. G.	2,070	23 (476)	80 (1,656)	103	69	—
B. J.	555	23 (127)	83 (460)	106	86	18
F. Wi.	1,653	36 (595)	63 (1,041)	99	73	15
L. McE.	2,232	37 (825)	77 (1,718)	114	74	24
G. L.	1,700	34 (578)	75 (1,275)	109	62	11
F. We.	3,360	44 (1,478)	61 (2,049)	105	47	19
E. McD.	1,830	26 (475)	80 (1,464)	106	79	16
R. W.	3,234	31 (1,002)	78 (2,522)	109	61	33
J. H.	1,700	29 (493)	73 (1,241)	102	69	33
E. P.	1,020	22 (224)	54 (550)	76	47	39
D. T.	875	30 (262)	74 (647)	104	72	22
M. N.	1,485	68 (1,009)	46 (683)	114	60	26
H. C.	800	27 (216)	40 (320)	67	49	26
Possible Sjögren's syndrome						
C. H.	1,512	27 (408)	60 (907)	87	72	26
A. P.	4,620	27 (1247)	75 (3,465)	102	81	29
B. C.	3,315	27 (895)	72 (2,386)	99	84	28
A. A.	2,150	18 (387)	74 (1,591)	92	66	40
Normal values	2,400±800	22.1±6.9	79.5±16.2	101.6±11.5	64.3±13.7	16.7±4.3

* Absolute numbers of T and B cells are shown in parentheses.

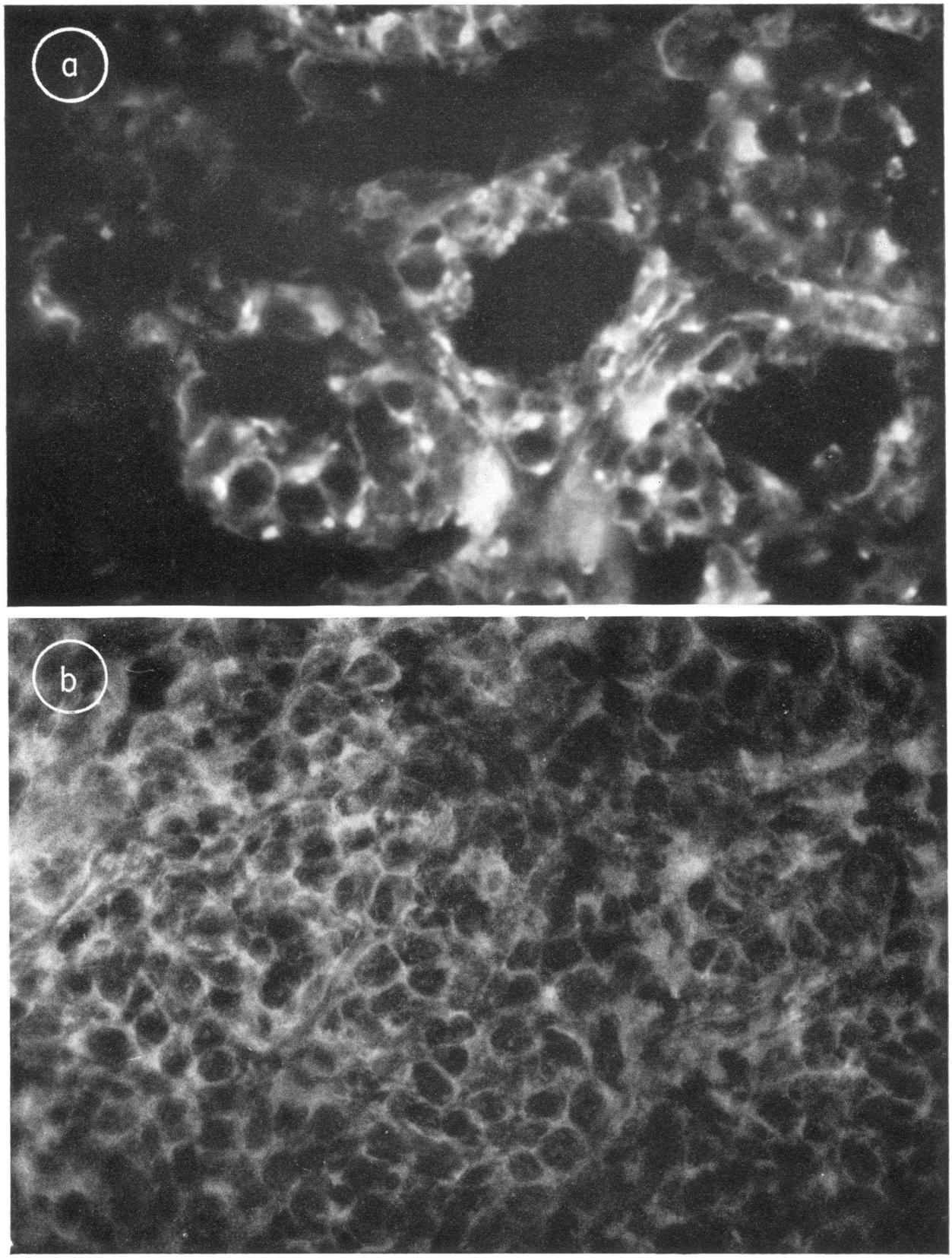
cubated with the same test lymphocytes produced no change.

Because it was felt possible that cell surface immunoglobulins detected by immunofluorescence in these patients might be influenced by cell binding of γG secondary to reaction with cell surface γM rheumatoid factor in a situation similar to that previously described by Preud'homme and Seligmann (37), several experiments using fluorescein-conjugated aggregated IgG were performed using Sjögren's patients' lymphocytes showing high percentages of surface IgM. No capping phenomena or positive demonstration of cell surface-bound rheumatoid factor could be conclusively demonstrated using these techniques. Lymphocytes from two patients were studied before and after incubation at 37°C for 16 h. There was no significant reduction in surface immunoglobulins as a consequence of incubation.

T cells in salivary glands. Labial biopsies were carefully examined using indirect immunofluorescence and rabbit anti-human thymocyte antiserum. In many instances striking accumulations of T lymphocytes were noted in the tissue lesions (Fig. 2). These infiltrations of T cells seemed clearly to be grouped in clusters or specific areas often particularly close to salivary ducts. Concomitant staining for B cells containing IgG, IgA, or IgM indicated clusters of cells in more patchy and different distribution which stained for these immunoglobulins in their cytoplasm. When histologic grading using a quantitative focus score technique was compared to relative grading of T cell infiltration by indirect immunofluorescence, general correlation was noted as can be seen in Table IV.

DISCUSSION

Sjögren's syndrome is a pivotal disease that links the benign lymphoid infiltration of the rheumatic disorders with the more malignant forms of lymphoproliferation. The salivary gland infiltrates characteristic of this ill-


a
b

ness have features of a benign process. In a previous study, we emphasized the relationship between these lymphoid infiltrates and those seen in the synovium in rheumatoid arthritis (8). Both are capable of producing large amounts of immunoglobulins and rheumatoid factor (8, 20, 22).

Patients with SS have a predilection to develop monoclonal gammopathies, always of the IgM class. There are at least seven published reports of coexisting SS and Waldenström's macroglobulinemia (5). In one patient, pulmonary lymphoid infiltrates and a monoclonal IgM appeared simultaneously and subsided together in response to corticosteroids (4). The present report extends these observations and demonstrates the increased number of B cells (particularly IgM) present in a majority of patients with SS. Increased numbers of B cells with surface IgM were most prominent in patients with definite SS and absent in three of four patients with possible SS. Why are these cells present in such large numbers in the circulation? What are the conditions that favor their proliferation into malignant B cells and the production of monclonal IgM?

No evidence for monoclonal IgM on the surface of these cells was obtained. In double staining studies using fluorescein conjugated anti-kappa and anti-lambda reagents and rhodamine-conjugated anti-IgM staining, some IgM-positive cells were found to be kappa-type whereas others were found to contain lambda light chains. This was true even in patient E. P. who had a serum monoclonal IgM. E. P. differs from the majority of cases of Waldenström's macroglobulinemia studied by Preud'homme and Seligmann who had monoclonal IgM on the surface of B cells (38). Perhaps in SS, where the monoclonal IgM is produced locally by cells infiltrating the salivary glands (7), these cells tend to remain in the tissues rather than to circulate in the blood.

In an earlier study of phytohemagglutinin reactivity and sensitization to dinitrochlorobenzene in SS, we reported evidence of decreased cellular immunity in two groups of patients, those with associated rheumatoid arthritis or generalized lymphoproliferation (39). The present study supports these observations by finding decreased numbers of T cells in three of five patients with associated SS and rheumatoid arthritis and in the patients with pseudolymphoma and macroglobulinemia.

SS occurs in 15% or more of patients with rheumatoid arthritis (40). Williams et al. noted that patients with rheumatoid arthritis ranged into two groups according to whether T cells were normal or decreased (28). The latter group tended to have the most active disease. Since T cells were decreased in 60% of our patients with coexisting SS and rheumatoid arthritis, it is probable that many patients with rheumatoid arthritis and low T cells have SS.

TABLE IV

Correlation Between Focus Score and Number of T Cells in Labial Biopsies

Patient	Focus score	Number of T cells
C. H.	0	0
A. P.	0.4	1+
R. W.	1.2	1+
M. H.	1.7	2+
E. McD.	2.3	2+
H. C.	4.2	2+
L. McE.	6.0	2+
J. H.	10.0	4+
D. T.	>10.0	2+
B. J.	>10.0	4+

The number of foci of 50 or more mononuclear cells per 4 mm^2 were counted and the score determined on the basis of total area of the specimen. The numbers of *T* cells were graded on a scale of 1–4 in which 1 represents 1–25% of the total cells, 2 is 25–50%, 3 is 50–75%, and 4 is over 75%. 20 high power fields were examined and 200–300 cells counted.

It is noteworthy that patients who have the most active salivary gland disease may have perfectly normal percentages of peripheral blood B and T cells, like B. J. in this study who has suffered from perisistent bilateral parotid gland swelling for over 1 y. These are also patients with normal cellular immunity (39).

Knowledge of the T or B cell nature of the salivary gland lymphocytes might be an important clue to the pathogenetic mechanism operating in SS. Immunoglobulin synthesis and immunofluorescent studies (7, 8) indicate the presence of B cells. The present study indicates as well the presence of T cells. In B. J., for example, the severe and extensive infiltrate is composed of large numbers of T cells (Table IV). In D. T., whose infiltrate is just as extensive, there are fewer numbers of T cells. Certainly, in different patients, the relative numbers of B and T cells may vary considerably and perhaps variations occur in the same patient at different points in time.

The large numbers of T cells, particularly in some heavily infiltrated lesions, suggests a role for cell medi-

FIGURE 2 Representative immunofluorescent photographs of labial biopsy specimens from patients with SS examined by indirect immunofluorescence (stained with rabbit anti-human thymus antiserum and fluorescein conjugated goat anti-rabbit immunoglobulin IgG). The majority of periductal infiltrating cells in Fig. 2*a* appear to be T cells showing clear membrane staining; 2*b* shows another view of a rather massive periductular infiltrate composed of T cells in another patient. (Magnification × 600)

ated immunity. The nature of the antigenic stimulus drawing these T cells into the tissue sites is not known but their presence should encourage additional studies of this question.

In this regard, recent studies of Marek's disease in chickens seem highly pertinent. In genetically susceptible birds, a herpes-type virus can bring on a lymphoid infiltrate of peripheral nerves or visceral lymphoid tumors. Rouse, Wells, and Warner have recently shown by autoradiography that 90% or more of the lymphocytes in the nerve lesions and tumors are T cells reactive with specific antiserum (41). They postulate a T cell mediated immunologic attack directed against epithelial cell surface antigens altered as a consequence of virus infection.

It seems likely that large numbers of T cells are also present in the synovium and synovial fluid in rheumatoid arthritis. Their demonstration in synovial fluid has recently been achieved using a rosette assay system (42). The improvement in rheumatoid arthritis that follows removal of lymphocytes by thoracic duct drainage (43), including decreased size of rheumatoid nodules, also suggests a role for T cells in the pathogenesis of rheumatoid arthritis.

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