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HISTOPATHOLOGICAL STUDIES OF THE LABIAL SALIVARY GLANDS IN PATIENTS WITH SJÖGREN'S SYNDROME PART I: LIGHT MICROSCOPIC STUDY

BY

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ABSTRACT

Labial salivary gland biopsy specimens from 111 patients evaluated for Sjögren's syndrome (SjS) were examined histopathologically with particular attention to the degree of lymphoid cell infiltration with or without the formation of epimyoepithelial islands, fibrosis and atrophy with fatty replacement. These cases were divided into groups, and the histological findings were compared. In definite cases, "positive" findings of more than one focus of lymphoid cells per lobule were seen in about 80%, this value closely coinciding with the reports in Europe and America. Epimyoepithelial islands and hyaline-like substance were also found in the cases with severe lymphoid cell infiltration. Cases of probable SjS, connective tissue disease and some other conditions showed lymphoid cell infiltration to a lesser degree. It seems likely that fibrosis and atrophy with fatty replacement are not closely related to SjS.

In several cases of definite SjS, labial salivary gland examinations after more than a one year interval were performed on two occasions, and the clinical and histopathological changes were investigated.

INTRODUCTION

In 1933, Sjögren, a Swedish ophthalmologist, published a monograph [1] describing in detail the clinical and histopathological features of 19 patients with keratoconjunctivitis sicca in the middle aged women with arthritis. Since then numerous papers have been published by many workers on the various different aspects of these conditions, named Sjögren's syndrome (SjS).

Generally, SjS consists of xerostomia and keratoconjunctivitis sicca with or without connective tissue disorder, often rheumatoid arthritis, occasional systemic lupus erythematosus, progressive systemic sclerosis, polyarthritis nodosa, etc. And it is recognized that some patients may develop extrasalivary abnormalities, including malignant lymphoma. In the advanced cases of SjS, marked atrophy of the systemic exocrine glands appears and is often associated with pathophysiological and morphological disorders of many other organs. However, individual cases commonly fail to exhibit all these features. Although SjS chiefly occurs in postmenopausal women, its presence in the female adolescents has been reported. Its course is long, symptomatic remissions occur and death can rarely be attributed to the syndrome itself.

In recent years, various disorders have been found to have an immunological basis, and it has been suggested that immunological processes may well play a role in the pathogenesis of this syndrome (Jones [2],

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Bunim [3], Bertram and Halberg [4], Leventhal [5], MacSween *et al.* [6], Cummings *et al.* [7], Berry *et al.* [8], Anderson *et al.* [9], Smith *et al.* [10]).

There are numerous methods for quantifying the extent of the disease in SjS. The salivary flow rate (Chisholm and Mason [11], Daniels *et al.* [12]), scintigraphy (Abramson *et al.* [13], Schall *et al.* [14]), sialography (Rubin and Holt [15], Park and Mason [16]), analysis of the secreted saliva (Benedek-Spät *et al.* [17], Mandel and Baurmash [18]) and salivary gland biopsy have all been used in the examination of the oral component in SjS. Of these, sialography and salivary gland biopsy are the most commonly performed in establishing a diagnosis.

Detailed histopathological changes in the major salivary glands were described by Godwin [19], Morgan and Castleman [20], Morgan [21], Cardell and Gurling [22], Bloch *et al.* [23] and Evans and Cruickshank [24]. The changes include marked infiltration of the lymphoid cells, atrophy of the acinar parenchyma, destruction and/or proliferation of the duct epithelial cells, and formation of the epimyoepithelial islands. These findings are most prominent in the major salivary glands, and parotid gland biopsy has been performed on many patients with SjS in order to provide a histopathological confirmation of the diagnosis. However, since this technique is painful and surgical injury is large, an alternative source of tissue is desirable.

Recently, the major and minor salivary glands in SjS have been considered to present the same characteristic histopathological appearance, and several investigators have discussed the usefulness of the minor salivary glands as a diagnostic aid in this condition (Cifarelli *et al.* [25], Chan [26], Bertram [27], Sliwowska [28], Eisenbud *et al.* [29], Calman and Reifman [30], Whaley *et al.* [31], Chisholm and Mason [32], Bertram and Hjörtig-Hansen [33], Daniels *et al.* [34], Davies *et al.* [35], Greenspan *et al.* [36] and Tarpley *et al.* [37]). However, there are very few papers reporting on the histological examination of the minor salivary glands on more than two occasions after a certain interval in same patient with SjS.

Part I of this study investigates the correlation between the histopathological findings of the labial salivary glands and the clinical manifestations in 111 patients with SjS and other conditions.

Materials and Methods

Labial salivary glands, biopsied from 96 female and 15 male patients, were studied. Their ages at the time of biopsy ranged from 16 to 68. The diagnosis of SjS was based on the criteria of Sjögren's Disease Research Committee of the Ministry of Health and Welfare in Japan [38].

The biopsied materials were fixed in 10% neutral buffered formalin for 24 hours, embedded in paraffin, and serial sections, 5 μ in thickness, were prepared for microscopic examination.

As indicated in Table 1, the cases were divided into 4 groups: A) definite cases of SjS, B) probable cases of SjS, C) cases of connective tissue disease and D) other cases. Definite cases of SjS were classified into 3 subgroups. Group I: sicca alone, Group II: sicca with connective tissue disease-like symptoms such as arthralgia and Raynaud's phenomenon, Group III: sicca with connective tissue disease.

The labial salivary glands in each group and subgroup were histopathologically examined with particular attention to the degree of lymphoid cell infiltration with or without the formation of epimyoepithelial islands, amount of fibrosis and atrophy with

Table 1. Clinical Groups of Patients with Labial Salivary Gland Biopsy

A)	Definite cases of SjS: 67 cases
	(mean age: 46.5-year-old, female: 63 cases, male: 4 cases)
	Group I: Sicca alone 32 cases
	(mean age: 48.7-year-old, female: 31 cases, male: 1 case)
	Group II: Sicca with connective tissue disease-like symptoms 16 cases
	(mean age: 46.4-year-old, female: 15 cases, male: 1 case)
	Group III: Sicca with connective tissue disease 19 cases
	(mean age: 44.9-year-old, female: 17 cases, male: 2 cases)
	RA: 12 cases, SLE: 2 cases, Hashimoto's thyroiditis: 2 cases, interstitial pneumonia: 1 case, overlap case: 1 case.
B)	Probable cases of SjS: 8 cases
	(mean age: 50.1-year-old, female: 4 cases, male: 4 cases)
C)	Cases of connective tissue disease: 11 cases
	(mean age: 39.5-year-old, all cases are female)
	SLE: 3 cases, Hashimoto's thyroiditis: 3 cases,
	RA: 2 cases, overlap cases: 2 cases, PSS: 1 case.
D)	Others
	I: Cases with subjective sicca symptom only, with no abnormalities of examination and no association with other disease 12 cases
	(mean age: 48.3-year-old, female: 10 cases, male: 2 cases)
	II: Cases with abnormal tastes, fatigability and irritability of eyes, etc, without subjective sicca symptoms 13 cases
	(mean age: 46.8-year-old, female: 8 cases, male: 5 cases)

fatty replacement. Lymphoid cell infiltration was evaluated according to the following grading system: Grade (−): well defined acini and ducts with no infiltration of lymphocytes and plasma cells; Grade (±): very slight infiltration of lymphocytes and plasma cells; Grade (+): 1 or 2 foci of lymphocytes and plasma cells (1 focus was considered to be an aggregation of 50 or more lymphocytes and plasma cells) (Fig. 4); Grade (++): 3 or more foci per lobule, or diffuse rather than aggregate infiltration extending to less than 1/2 of the lobular area (Fig.5); Grade (+++): marked infiltration of lymphocytes and plasma cells with replacement of acinar parenchyma extending to more than 1/2 of the lobular area (Fig. 6). Fibrosis and atrophy with fatty replacement were subjectively graded as follows: Grade (−) as absent, Grade (±) as very slight, Grade (+) as extending to less than 1/4 of the lobular area, Grade (++) as extending to 1/4 and 1/2 and Grade (+++) as extending to more than 1/2 (Fig. 7, 8).

Five cases of SjS have undergone labial salivary gland biopsies on two occasions after intervals of more than a one year. And 2 autopsy cases of SjS had a previous labial salivary gland biopsy while alive. The clinical and the histopathological changes were also compared in these 7 cases.

Results

I. Grade of lymphoid cell infiltration

Biopsied labial salivary glands showed variable degrees of lymphoid cell infiltration and acinar atrophy, ranging from almost normal acinar tissue to complete parenchymal atrophy due to the replacement by the infiltrated cells. In the cases with very slight changes (±), scattered lymphocytes and plasma cells were found among the acini, periductal and perivascular areas. In the Grade (+) cases, there were 1 or 2 foci chiefly composed of lymphocytes in the periductal areas in the vast majority of cases

(Fig. 4), and scattered plasma cells in the periphery of the foci or throughout the glandular stroma. In some foci, plasma cells were more dominant than the lymphocytes, but in the large foci and severe cases, lymphocytes outnumbered the plasma cells. In the Grade (++) cases, focal and diffuse lymphocytic infiltration was more prominent in the periductal areas and parenchyma combined with atrophy and disappearance of acini (Fig. 5), and dilatation of the lumen with flattened epithelial cells, destruction and/or hyperplasia of the epithelial cells of the intercalated and intralobular ducts were noted. In some areas, destruction of the duct wall and basement membrane with leaking saliva were also found. Furthermore, in the Grade (+++) cases, cell infiltration extending to more than 1/2 of the lobular areas (Fig. 6) and occasional lymph follicles were found (Fig. 9). The severity of lymphoid cell infiltration was different in each lobule of the same gland. There was no evidence of neutrophilic cell infiltration. The remaining ducts in aggregations of lymphoid cells in some of the Grade (++) and (+++) cases showed cellular hyperplasia with loss of cellular polarity and narrowing of the lumen, and conglomeration of epithelial cells (Fig. 10) called "epimyoepithelial islands" were noted. Lymphocytes and plasma cells also infiltrated among these proliferated epithelial cells. In some Grade (++) and (+++) cases, a small amount of a hyaline-like substance, which stained pink with hematoxylin and eosin, appeared in and around the proliferated epithelial masses (Fig. 11). The results of various kinds of stains on this hyaline-like substance were as follows: PAS: positive without diastase digestion, Mucicarmine: negative, Alcian-blue: negative, PTAH: negative, PAM: negative, Elastica van Gieson: yellow-red, Azan Mallory: pale blue and Masson's trichrom: green.

Oncocytic changes were present in most cases with an equal distribution and appeared not to be correlated with SjS.

The histopathological differences between each group and subgroup mentioned earlier are summarized as follows:

A. Definite cases of SjS

Comparison of the degree of lymphoid cell infiltration in each group of definite SjS is shown in Table 2 and Fig. 1. "Positive" findings (more than Grade (+)) in the labial salivary glands were seen in 26 of 32 cases (81.3%) in Group I, 12 of 16 cases (75.0%) in Group II and 16 of 19 cases (84.2%) in Group III. The lymphoid cell infiltration in each specimen had a tendency to be more frequent in the specimens of Group III, less

Table 2. Prevalence of Lymphoid Cell Infiltration in the Labial Salivary Glands in Each Group of Definite Sjögren's Syndrome ( ): %

Group	No. of caces	(−)	(±)	(+)	(++)	(+++)	More than (+)
I	32	1 (3.1)	5 (15.6)	13 (40.6)	7 (21.7)	6 (18.8)	26 (81.3)
II	16	0 (0.0)	4 (25.0)	5 (31.3)	4 (25.0)	3 (18.8)	12 (75.0)
III	19	0 (0.0)	3 (15.8)	5 (26.3)	6 (31.6)	5 (26.3)	16 (84.2)
total	67	1 (1.5)	12 (17.9)	23 (34.3)	17 (25.4)	14 (20.9)	54 (80.6)

Group I: Sicca alone, Group II: Sicca with connective tissue disease-like symptoms, Group III: Sicca with connective tissue disease

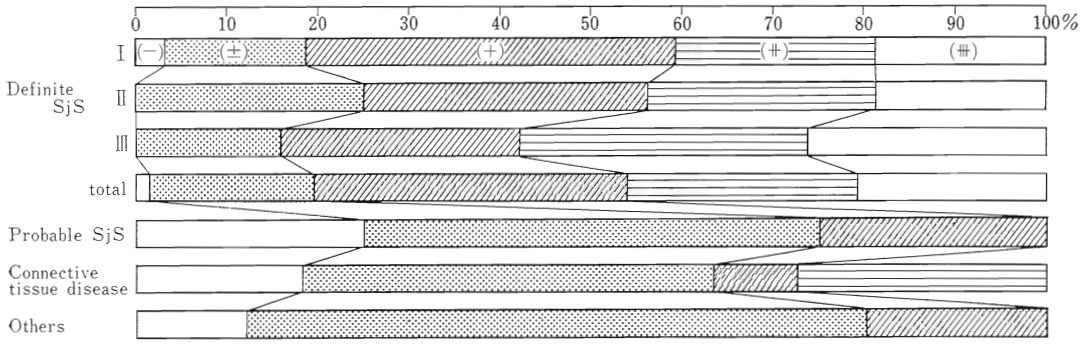

Fig. 1. Lymphoid Cell Infiltration in the Labial Salivary Glands in Each Group

in Group I and still less in Group II, but these differences had no statistical significance. The total prevalence of "positive" findings in definite SjS adding Groups I, II and III were 54 of 67 cases (80.6%). Although the greatest lymphoid cell infiltration (+++) was most frequent in Group III, this study showed no important difference in frequency in all these groups. In the 4 male cases with definite SjS, the degree of lymphoid cell infiltration in each was Grade (+).

Epithelial hyperplasia of the ducts, epimyoepithelial islands and deposits of hyaline-like substance appeared in the cases of more than Grade (++): epimyoepithelial islands or analogous structures were found in 16 cases, and deposits of hyaline-like substance were found in 6 cases.

B. Probable cases of SjS

In 8 cases with probable SjS, the degree of lymphoid cell infiltration was as follows: 1 Grade (−) case, 5 Grade (±) cases, 2 Grade (+) cases and no Grade (++) and (+++) cases. These 2 Grade (+) cases had very mild sicca symptoms and no remarkable changes in the sialographic findings and by other examinations.

C. Cases of connective tissue disease

In these 11 cases, the degree of lymphoid cell infiltration was as follows: 2 Grade (−) cases, 5 Grade (±) cases, 1 Grade (+) case, 3 Grade (++) cases and no Grade (+++) case. The diagnosis of the positive cases consisted of 2 SLE and 2 Hashimoto's thyroiditis.

D. Twelve cases with subjective sicca symptoms with no noticeable laboratory abnormalities and no association with other diseases

The degree of lymphoid cell infiltration was Grade (−) or (±), and more than Grade (+) was not noted. The details of the subjective sicca symptoms were 8 cases of dry mouth, 2 cases of dry eye and 2 cases of both symptoms.

E. Thirteen cases with abnormal tastes, fatigability and irritability of eyes, etc, without sicca symptoms

There were 1 Grade (−) case, 7 Grade (±) cases and 5 Grade (+) cases. The Grade (+) cases complained of fatigability and irritation of eyes, abnormal tastes, arthralgia and swelling of the major salivary glands.

II. Fibrosis and atrophy with fatty replacement

Fibrosis was often seen, partially or even entirely involving the lobules. Fibrosis usually began at the lobular peripheral, septal and periductal areas, and diffusely developed into the parenchyma with atrophy of the acini. In the advanced cases, acinar parenchyma was completely replaced by the fibrous tissue with the so-called

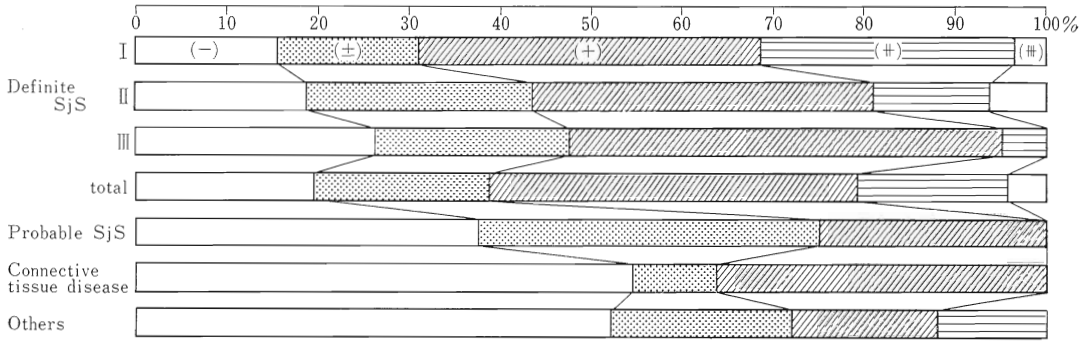

Fig. 2. Prevalence of Fibrosis of the Labial Salivary Glands in Each Group

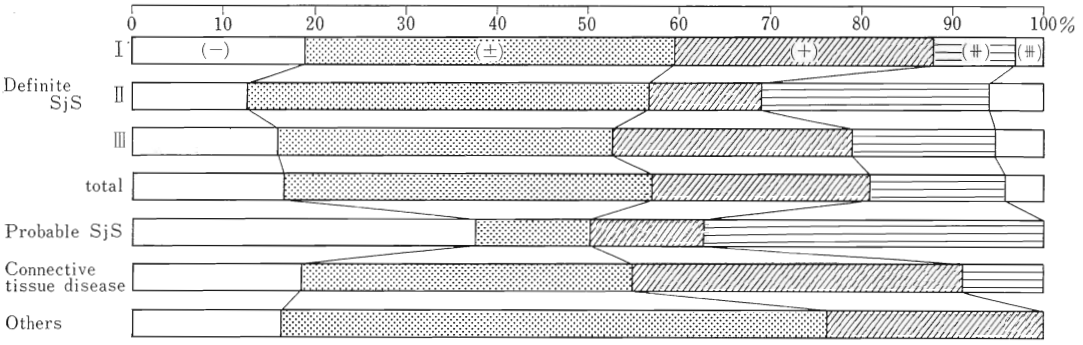

Fig. 3. Prevalence of Atrophy with Fatty Replacement of the Labial Salivary Glands in Each Group

canalicular regression or tubular metaplasia (Fig. 7). Atrophy with fatty replacement, when present, was seen in the lobular peripheral and septal areas. In advanced atrophy with fatty replacement, most of the acinar parenchyma disappeared, and only a few large excretory ducts and peripheral connective tissue of the lobules remained (Fig. 8). The degree of fibrosis and atrophy with fatty replacement were different in each lobule, e.g. some lobules showed extensive involvement while the adjacent ones were spared. In the cases of slight to moderate fibrosis and atrophy with fatty replacement, various degrees of lymphoid cell infiltration were associated. However, in the severe cases, lymphoid cell infiltration was reduced.

The degree of fibrosis in each case is shown in Fig. 2. In the definite cases of SjS, fibrosis of more than Grade (+) were seen in 50 to 70% of the cases and was especially prominent in sicca alone. On the other hand, in the cases of probable SjS and non-SjS, more than Grade (+) were seen in 25 to 35%, and there was no severe fibrosis in any of these cases.

The degree of atrophy with fatty replacement in each case is found in Fig. 3. Findings with more than Grade (+) were seen in 40 to 50% of the cases of definite SjS, probable SjS and connective tissue diseases. Findings with more than Grade (++) were frequent in the cases of sicca with connective tissue disease-like symptoms and probable SjS, while there were no more than Grade (++) in the cases of non-SjS without any other disease.

III. Seven cases, in which the histopathological examinations of the labial salivary glands were performed on two occasions at intervals of more than a one year

Case 1 (S. T.): A 41-year-old female had a gradual onset of swelling of the bilateral parotid gland, dry eye and arthralgia, and was diagnosed as definite SjS by the laboratory data, sialography and labial salivary gland biopsy 3 years before. Histology of the labial salivary glands at that time demonstrated marked lymphoid cell infiltration with complete parenchymal replacement and scattered epimyoepithelial islands (Fig. 12-a). During the 6 months from the onset, steroid drugs were administrated and the parotid swelling disappeared. Later, sicca symptoms continued without any association with the other connective tissue diseases. Re-biopsy was performed after 1 year and 8 months. The degree of lymphoid cell infiltration was less than that of the previous biopsy, though it had now extended to all of the lobules (Fig. 12-b).

Case 2 (S. I.): A 46-year-old female noted the onset of dry mouth and eye, which continued since 9 years ago. During that time, she was treated for Hodgkin's disease with chemotherapy. Biopsy of the labial salivary glands showed slight to moderate focal and diffuse lymphoid cell infiltration in the periductal areas with fibrosis. Seventeen months later, she was readmitted because of pulmonary tuberculosis, and re-biopsy of the labial salivary glands was performed in order to follow-up SjS at this time. Histopathologically, periductal lymphoid cell infiltration and fibrosis were observed, and they showed no improvement over her previous condition.

Case 3 (M. K.): A 41-year-old male had a 5 to 6-year-history of dry eye. A diagnosis of conjunctivitis was made by an oculist. SjS was also suspected, but the evidence was insufficient to make or exclude a positive diagnosis. Biopsy of the labial salivary glands at that time showed no lymphoid cell infiltration and dilatation of the main ducts. He was treated conservatively, but symptoms of marked dry eye continued. A second examination was performed after 1 year and 7 months. The labial salivary glands showed severe fibrosis with scantly lymphoid cell infiltration in part. A definite diagnosis of SjS had not been made by the time of this study.

Case 4 (T. U.): A 47-year-old female who noted the onset of dry eye 17 months before, subsequently developed dry mouth, arthralgia and general fatigue, and was diagnosed as a case of autoimmune hepatitis and SjS by detailed examinations. The labial salivary glands showed marked lymphoid cell infiltration in the periductal areas associated with epithelial hyperplasia of the ducts (Fig. 13-a), fibrosis and atrophy with fatty replacement in part. The general symptoms were controlled by steroid treatment. After 1 year, re-biopsy was performed in order to follow-up SjS. Lymphoid cell infiltration was decreased compared with the previous biopsy, but an increase of diffuse fibrosis with acinar atrophy was present (Fig. 13-b).

Case 5 (K. Y.): A 27-year-old female had a 10-year-history of bilateral intermittent swelling of the parotid glands. A diagnosis of SLE was made and association with SjS was suspected, though the sicca symptoms were very mild. Labial salivary glands demonstrated periductal lymphoid cell infiltration with epithelial hyperplasia and destructive changes of the ducts (Fig. 14-a). After 1 year and 3 months, the second biopsy revealed complete replacement of the acinar parenchyma with lymphoid cell

infiltration, fibrosis and fatty tissue (Fig. 14-b). During this period, she had continuously received steroid treatment.

Case 6 (H. T.): A 56-year-old female developed Raynaud's phenomenon, general fatigue, sclerosis of the finger, dry eye and jaundice 12 years before, and she was diagnosed as having hepatitis at that time. Three years ago, a definite diagnosis of primary biliary cirrhosis, SjS and sclerodactylia were made by the biopsies of the liver, salivary gland and skin. Labial salivary gland sections showed marked lymphoid cell infiltration with the formation of epimyoepithelial islands and deposits of hyaline-like substances. She was treated conservatively, but her condition progressively deteriorated and she died 2 years later. The direct causes of death were listed as liver dysfunction and widespread military tuberculosis. Autopsy revealed typical histological findings of SjS in the major salivary glands, but slight lymphoid cell infiltration with diffuse fibrosis in the labial salivary glands.

Case 7 (K. Y.): A 35-year-old female developed arthralgia, swelling of the general lymph nodes and Raynaud's phenomenon 12 years before, and also noted dry eye and dry mouth 6 years later. The labial salivary gland biopsy at that time showed marked periductal lymphoid cell infiltration with epithelial hyperplasia (Fig. 15-a), and a diagnosis of definite SjS was made. Subsequently steroid treatment was instituted. However, the condition did not improve and was complicated by SLE 4 years ago. Although she was receiving large doses of steroid drugs, deterioration ended in death. The causes of death were reported to be renal failure and systemic fungal infection. At autopsy, major salivary glands showed marked atrophy with fatty replacement and focal lymphoid cell infiltration in part. Labial salivary glands showed slight to moderate focal and diffuse lymphoid cell infiltration (Fig. 15-b).

Discussion

I. Lymphoid cell infiltration and its frequency: Many investigators have reported that cell infiltration found in the major and minor salivary glands in the patients with SjS consists primarily of lymphocytes and they have devised different criteria for establishing the histopathological grades. Of late, in evaluating the grade of lymphoid cell infiltration in the minor salivary glands, the focus score-method, which is devised by Chisholm *et al.* [32, 39], is widely utilized. Their method has five steps as follows: 0: absent, 1: slight infiltration, 2: moderate infiltration of less than 1 focus, 3: 1 focus (a focus consists of an aggregation of 50 or more lymphoid cells) and 4: more than 1 focus. Chisholm *et al.* investigated the labial salivary glands obtained from the patients with SjS, other connective tissue diseases and other conditions, and they believed that Grades 3 and 4 were the characteristic "positive" findings of the minor salivary glands in patients with SjS. Grades 3 and 4 in their criteria correspond to more than Grade (+) in this study.

The frequency of the "positive" findings of lymphoid cell infiltration in the minor salivary glands in SjS have been reported by many investigators. In this study, 80.6% of the labial salivary glands in definite SjS are histologically "positive", and this value coincides closely with the other reports.

Comparing the degree of lymphoid cell infiltration in the cases of sicca alone, sicca with connective tissue disease and connective tissue disease without sicca, several investigators have reported that its frequency and severity were greater in sicca alone, less

in sicca with connective tissue disease, and still less in the other connective tissue diseases without sicca (Sliwowska *et al.* [28], Daniels *et al.* [34], Davies *et al.* [35], Greenspan *et al.* [36], Tarpley *et al.* [37]). Conversely, Whaley *et al.* [31] showed that lymphoid cell infiltration was more frequent in sicca with rheumatoid arthritis than in sicca alone. On the other hand, Eisenbud *et al.* [29] reported that though lymphoid cell infiltration was seen in 82%of the palatal salivary glands in the various connective tissue diseases, there were no significant differences among them. Friedman *et al.* [40] also reported that there were primarily no differences in the histopathological changes of the minor salivary glands in SjS and other connective tissue diseases. In this study, although the greatest changes of Grade (##) were more frequent in sicca with connective tissue disease, significant differences in the frequency of "positive" findings were statistically negligible among the cases of sicca alone, sicca with connective tissue disease-like symptoms and sicca with connective tissue disease. Slight to moderate lymphoid cell infiltration was also found in some cases of connective tissue diseases and other conditions. Some authors reported that the lymphoid cell infiltration in the salivary glands might be found in not only SjS but also in the other connective tissue diseases (Eisenbud *et al.* [29], Friedman *et al.* [40]), or that such cases might represent an association with the early stage or subclinical state of SjS (Chisholm and Mason [23], Waterhouse *et al.* [41], Waterhouse and Doniach [42]). Further studies into this problem are necessary.

This study supports the findings of the other investigators (Bloch *et al.* [32], Greenspan *et al.* [36], Ishikawa *et al.* [43]) of the marked variation of lymphoid cell infiltration not only from lobule to lobule in the same gland but also from gland to gland in the same patient in the degree of involvement. Research into SjS would be facilitated if the biopsy specimens contained more salivary tissue than usually supplied.

II. Origin of the lymphoid tissue: The origin of the lymphoid tissue seen in the typical lesions in SjS is still a subject of speculation. Some investigators believed that these changes were the results of hyperplasia of the normally occurring lymphoid tissue of embryonic origin (Godwin [19], Yarington and Zagibe [44]). In fact, many studies have reported evidence that lymph nodes and their analogous structures are found in and around major salivary glands in the autopsy cases (Okabe [45]), and it seems reasonable to support that these tissues may be stimulated by a precipitating factor leading to some neoplastic changes. However, in the minor salivary glands, there are no specimens demonstrating an aberrent tissue (Ishikawa *et al.* [46]), although the histopathological changes of the minor salivary glands are closely similar to those in the major salivary glands in SjS. Therefore, it is thought that the lymphoid tissue in the salivary glands in SjS primarily originates from the infiltration and proliferation of the lymphoid cells.

Although the immunopathological investigation is not dealt with in this study, knowledge of infiltrated cell-nature may be one of the important clues to the pathogenetic mechanism operating in SjS. Taking into account the histopathological features of the salivary glands in SjS, it is reasonable to lean toward the immunologic basis for this disease and, indeed, recent immunological findings agree that SjS may be derived from autoimmune disorders. However, there are too few studies showing immunological identification of the infiltrated lymphoid cells and immunoglobulin synthe-

sis in the tissue section of the salivary glands. These infiltrated cells in the labial salivary glands appeared to be B-cells with local immunoglobulin synthesis, and some of the lymphocytes were T-cells and that the proportion of the T-cells in the foci increased with the increasing focus score (Talal *et al.* [47, 48], Chused *et al.* [49]).

III. Epimyoepithelial islands: Morgan and Castleman [20] described that one of the distinctive findings of SjS in the major salivary glands was the alteration of the ducts characterized by hyperplasia of the duct epithelial cells and gradual narrowing of the duct lumen resulting in the formation of compact cellular masses, called "epimyoepithelial islands", lying in the stroma of the lymphoid tissue. Several authors described that these epimyoepithelial islands were not found in the minor salivary glands in SjS (Eisenbud *et al.* [29], Chisholm and Mason [32], Davies *et al.* [35], Greenspan *et al.* [36], Talal and Bunim [50], Akin *et al.* [51]). However, Bertrum and Hjörtig-Hansen [33], Tarpley *et al.* [37] and Suzuki *et al.* [52] reported that the epimyoepithelial islands were also seen in the minor salivary glands in SjS. In the present study on the labial salivary glands, the epimyoepithelial islands and their analogous structures were noted in the serial sections of about one-half of the definite cases with more than Grade (++), however, it could not be clarified whether these islands originated from the duct epithelial cells, myoepithelial cell or both of them viewed by light microscopy.

IV. Hyaline-like substance: The hyaline-like substance, which appears in and around the altered ducts and epimyoepithelial islands, is frequently observed in the major salivary glands (Morgan and Castleman [20], Lucas and Thackray [53], Lucas [54]). In the labial salivary glands, Bertrum and Hjörtig-Hansen [33] reported that the hyaline-like substance was not encountered in the epimyoepithelial islands, and, on the other hand, Greenspan *et al.* [36] showed the accumulation of this substance around the altered ducts and blood vessels in many of the severe cases with confluent foci. In the present study, although the quantity was small, the hyaline-like substance was found in and around the altered ducts and epimyoepithelial islands in 6 cases of the definite cases with more than Grade (++). The origin and nature of this substance will be discussed in Part II, which is published in a separate paper.

V. On fibrosis and atrophy with fatty replacement of the minor salivary glands in SjS: Davies *et al.* [35] described that fibrosis and fatty replacement of the acinar parenchyma and tubular structures lined by the low columnar epithelium within the acinar fields were the common features in SjS and rheumatoid arthritis. On the other hand, Tarpley *et al.* [37] also reported that fibrosis and fatty replacement, minimal to heavy, were found in the labial salivary glands in their patients with SjS, but they pointed out that it was necessary to consider the general status such as diabetes mellitus, obesity, malnutrition or alcoholism, because these factors might have an effect on the salivary glands. However, even though fibrosis and fatty replacement are not characteristic in SjS, these findings suggest that severe inflammatory changes might have existed formerly in some cases. In the present study, although the detailed status and treatment in all cases could not be examined, severe fibrosis with conspicuous canalicular regression or so-called tubular metaplasia was seen in only the definite cases, while atrophy with fatty replacement, minimal to heavy, was seen in each group.

VI. Two occasions of labial salivary gland biopsy at intervals of more than a one

year: There are a few papers reporting on the histopathological examinations of the labial salivary glands on more than 2 occasions after a certain interval. Tarpley *et al.* [37] investigated several untreated patients with SjS who had been followed for over a period of time and had undergone more than 1 biopsy, and the histological findings in these patients were progressive in each succeeding biopsy procedure. Anderson *et al.* [55] showed that one-half of the patients who received cyclophosphamide therapy showed clinical and histological improvement. Ishikawa *et al.* [56] reported on a female case who had been suffering for 8 years from SjS and had endured 5 biopsies of the parotid and labial glands during this period. Histological findings of these biopsies did not show any improvement in the course of the disease. In the present investigation, 7 cases have been followed for over a period of time and have undergone twice histopathological examinations of the labial salivary glands after an interval of more than a one year. Four cases who have been treated with steroid drugs showed a decrease of lymphoid cell infiltration and a tendency to an increase of fibrosis and atrophy with fatty replacement. Untreated cases showed an increase of lymphoid cell infiltration in various degrees in each succeeding biopsy. Therefore, when the biopsied salivary glands are investigated, a more detailed past history and treatment than is usually supplied must be also considered to be necessary.

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Explanation of Plates

Plate 1.

Fig. 4: One or 2 foci of lymphoid cells in periductal areas per each lobule, graded as (+) (×50).
Fig. 5: Diffuse lymphoid cell infiltration extending ing to less than 1/2 of lobular area, graded as (++) (×50).
Fig. 6: Marked lymphoid cell infiltration extending to more than 1/2 of lobular area, graded as (+++) (×50).
Fig. 7. Marked fibrosis with so-called tubular metaplasia or canalicular regression of epithelium (×80).

Plate 2.

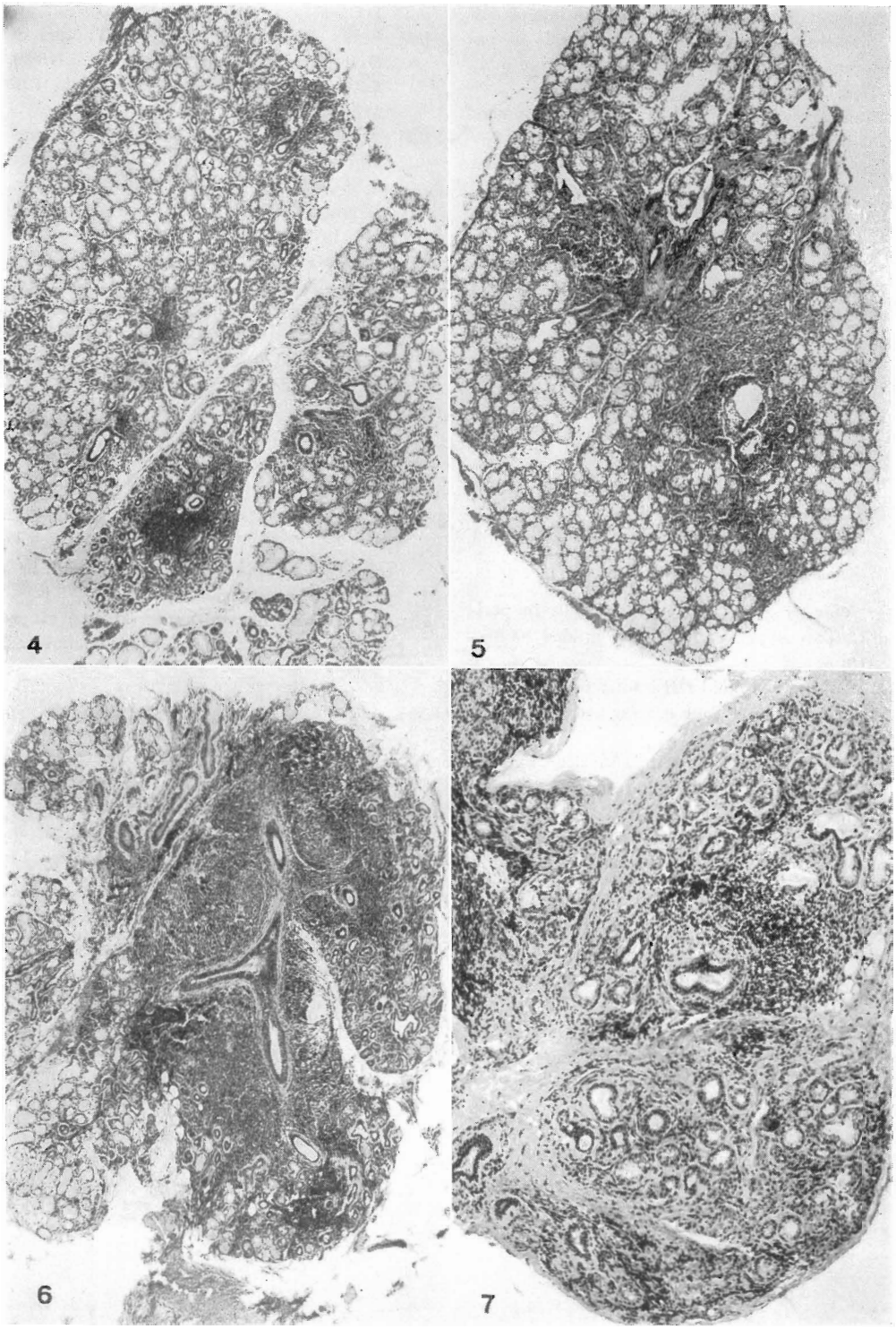
Fig. 8: Marked atrophy with fatty replacement (×50).
Fig. 9: Lymph follicles are found in a few severe cases (×120).
Fig. 10: Conglomeration of hyperplastic epithelial cells, called "epimyoepithelial islands", in lymphoid cell aggregation (×300).
Fig. 11: Hyaline-like substance (arrows) are noted in and around proliferated epithelial masses. (×500).

Plate 3.

Fig. 12-a: First biopsy of Case 1 (×300)
Fig. 12-b: Second biopsy of Case 1, after 1 year and 8 months (×300)
Fig. 13-a: First biopsy of Case 4 (×120)
Fig. 13-b: Second biopsy of Case 4, after 1 year (×120)

Plate 4.

Fig. 14-a: First biopsy of Case 5 (×120)
Fig. 14-b: Second biopsy of Case 5, after 1 year and 3 months (×120)
Fig. 15-a: Biopsy of Case 7 (×50)
Fig. 15-b: Autopsy of Case 7, after 6 years (×120)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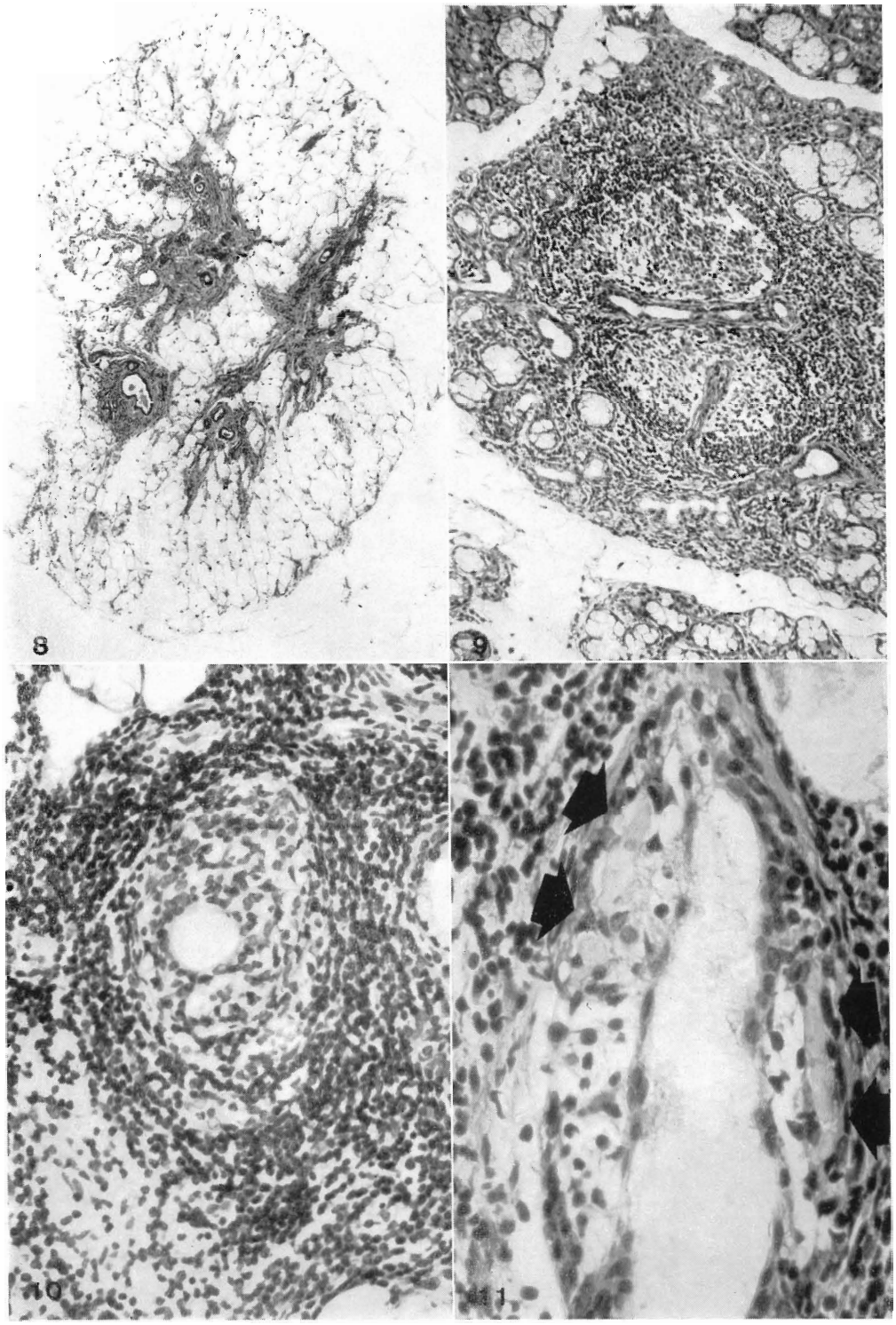
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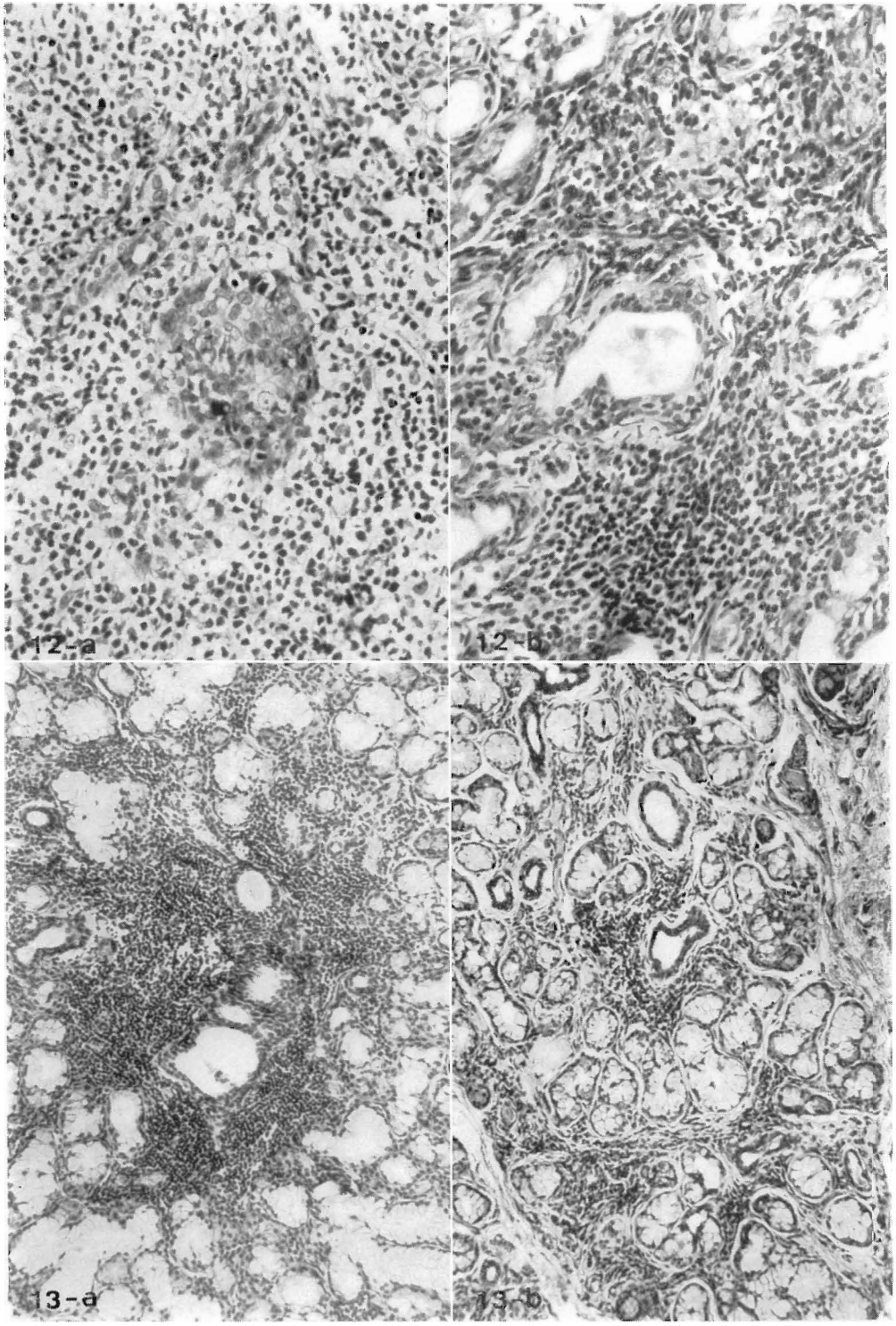
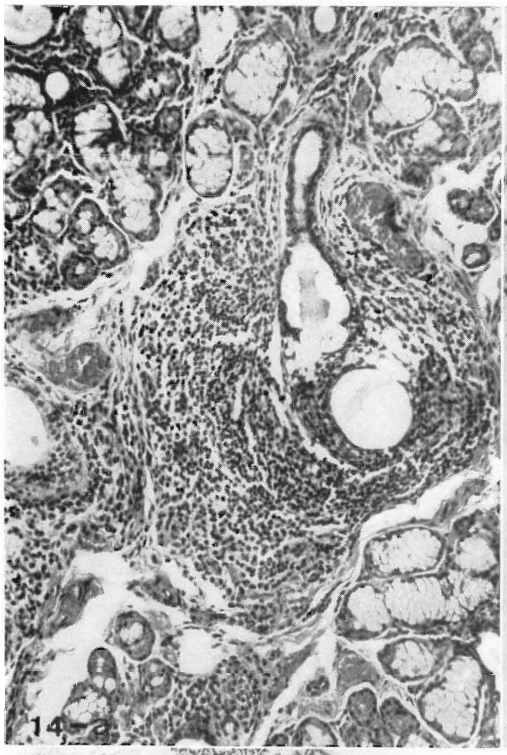

12-a
12-b
13-a
13-b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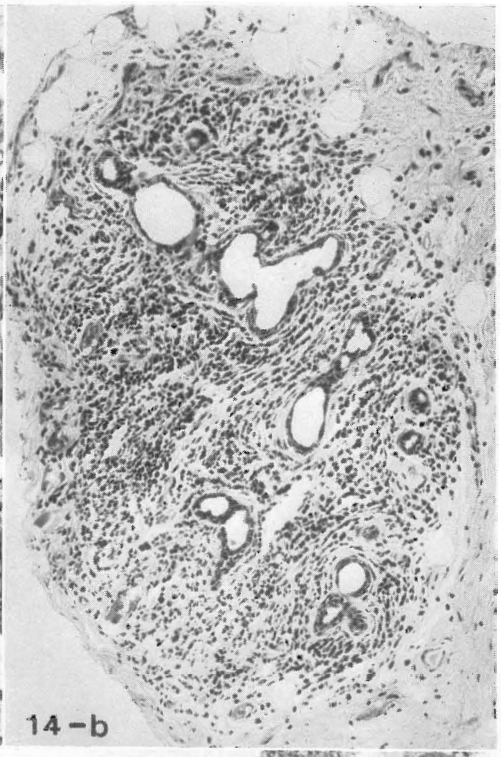
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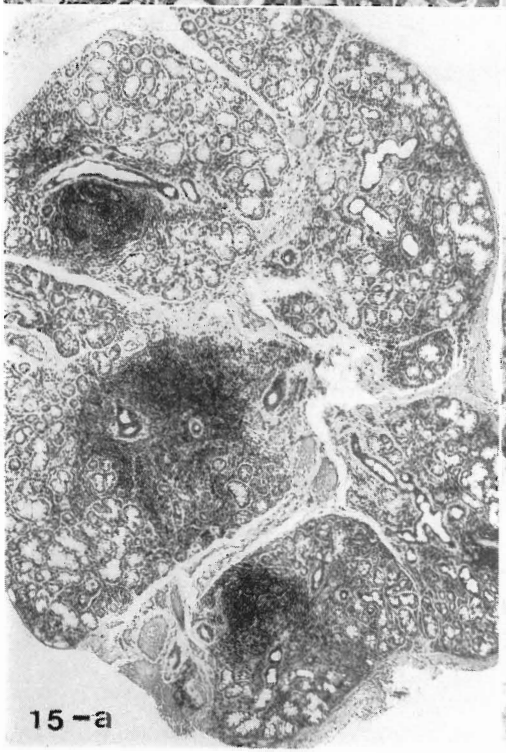
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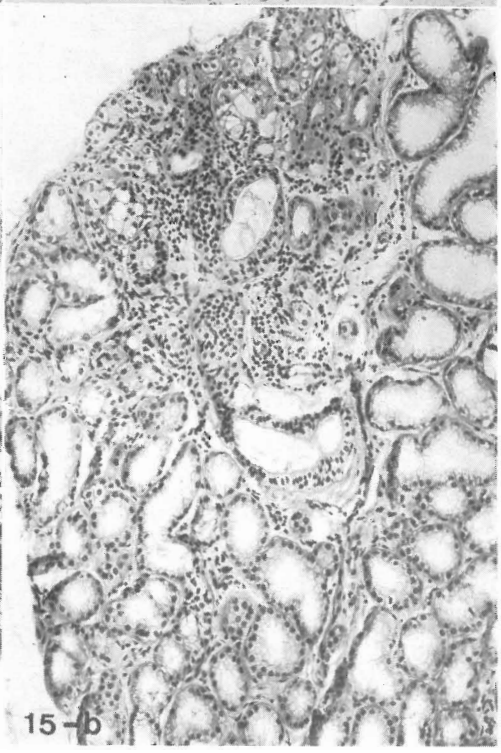
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