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HISTOPATHOLOGY OF LABIAL SALIVARY GLANDS IN SJÖGREN'S SYNDROME

BY

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ABSTRACT

The histopathology of labial salivary glands of 20 patients with Sjögren's syndrome was examined and compared with other clinical findings. All patients were women and their age ranged from 28 to 73. The diagnosis was based on clinical symptoms of dry mouth and dry eyes, and frequently rheumatoid arthritis. Sialography of the parotid gland was undertaken on 19 patients and showed characteristic sialectasis in 13 cases. Schirmer's test and Rose-Bengal staining were all positive. Waaler-Rose and latex fixation tests were used for the demonstration of rheumatoid factor and 15 cases were assumed to have rheumatoid arthritis.

The biopsy from labial salivary glands showed a variety of histopathologic appearances. The primary changes appeared to be periductal infiltration of lymphoid cells and dilatation of the ducts. As the lymphocytic infiltration increased in the glandular tissue, the secretary cells were beginning to disappear and the ducts became more prominent. Finally, the characteristic histopathological features of Sjögren's syndrome, germinal center and epimyoepithelial island, were found in 6 cases.

Results of examination on these cases suggested that the histopathology of the labial salivary glands would be a valuable diagnostic aid, if the results are considered with other clinical manifestations.

INTRODUCTION

The typical feature of Sjögren's syndrome is characterized by the triad of xerostomia, keratoconjunctivitis sicca, and a connective tissue disease, usually rheumatoid arthritis. In order to qualify for the diagnosis of Sjögren's syndrome two of the three main components, usually the first two, must be present[1-5].

Although there are various procedures for the diagnosis of xerostomia, such as salivary flowrate determination, secretory sialography, and scintigraphy, it is well known that the major salivary glands and lacrimal glands in Sjögren's syndrome represent characteristic histopathological figures[2,3,5], and it would be very valuable to obtain a major salivary gland or lacrimal

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gland for diagnosing Sjögren's syndrome. However, this cannot be justified because of the inconvenience to patients and the possible complication from the risk of facial nerve injuries or parotitis.

According to Cardell and Gurling[6], from the autopsy of postmortem examination of Sjögren's disease, the sections of the lacrimal, parotid, submandibular, sublingual, and submucous glands showed an essentially similar picture. Recently Chisholm et al.[7] have also found a correlation between the degree of lymphocytic infiltration in major and minor salivary glands in a deceased subject. From these facts, there is more than a suggestion that the presence of lymphocytic foci in the labial salivary glands in Sjögren's syndrome reflects the same histologic changes in other glands as a whole.

In order to ascertain the value of the clinical diagnosis of Sjögren's disease, we have tried to study the histopathology of minor salivary glands from lower lip instead of major salivary glands.

Materials and Methods

20 female patients with Sjögren's syndrome were studied at the department of the Second Oral Surgery in Tokyo Medical and Dental University. The age and sex distribution are shown in Table 1.

To establish the diagnosis of Sjögren's syndrome, two of the three major symptoms, that is, dry eyes, dry mouth, and connective tissue disease, were required[3]. The diagnosis in each patient was made when the clinical history and physical examination were consistent with these symptoms.

Oral examination: The clinical examination was made by questioning the patient for the presence of the dryness of the mouth. Sialography of the parotid gland was also carried out on 19 patients with 76% Urographin.

Ophthalmological examination: Keratoconjunctivitis sicca was diagnosed when a patient had diminished lacrimation, shown by Schirmer's test and Rose-Bengal staining. The Rose-Bengal test was used to detect corneal lesions.

Blood examination: In addition to routine laboratory findings, the Waaler-Rose and latex fixation tests were used for the demonstration of rheumatoid factor.

Biopsy from lower lip: The minor salivary glands of the lower lip were chosen for biopsy since they were easily accessible. After local anesthetic infiltration (2% Xylocaine), oral mucous membrane was incised to the muscle layer. Then, minor salivary glands were visible as yellow-white spots under the mucous membrane and the gland was pulled out and cut off at the base. The material was fixed in 10% Formallin, embedded in paraffin, and thin sections were prepared for microscopic examination.

Table 1. Clinical and laboratory finding in twenty patients with Sjögren's syndrome

Case No.	Name	Sex	Age (yrs)	Dry mouth	Dry eyes	Arthr-algia	Sialo-graphy	Schirmer test l(mm)	r	Rose bengal	RA	Waaler rose
1.	K.I.	F	53	+	+	+	+	1	1	++	+	
2.	K.T.	F	34	+	+	−	+	0	0	++	−	
3.	M.T.	F	54	+	+	−	+	5	9	+	−	
4.	R.H.	F	69	+	+	+	+	2	9	+	+	64×
5.	K.M.	F	52	+	+	+	+	1	1	+	+	32×
6.	C.T.	F	61	+	+	+	−	3	5	+	+	
7.	A.F.	F	46	+	+	+	+	7	7	+	++	64×
8.	T.M.	F	44	+	+	+	±	7	7	+	++	64×
9.	S.T.	F	42	+	+	+	±	5	4	+	++	64×
10.	S.I.	F	41	+	+	+	+	7	7	+	+	16×
11.	Y.M.	F	63	+	+	+	+	8	5	++	++	16×
12.	M.O.	F	48	+	+	+	+	2	2	+	+	16×
13.	S.T.	F	42	+	+	+	+	2.5	2.5	+	+	16×
14.	T.T.	F	52	+	+	+		2	2			8×
15.	K.Y.	F	28	+	+	+	+	3	1		+	64×
16.	R.S.	F	39	+	+	−	+	0	3	±	−	16×
17.	K.K.	F	53	+	+	−	+	1	0	+	+	64×
18.	S.T.	F	32	+	+	−	±	5	5		+	32×
19.	M.I.	F	63	+	+	+	±	5	7	+	+	16×
20.	M.T.	F	73	+	±	+	−	1	1	−	++	128×

Results

The clinical features in these 20 patients are outlined in Table 1. All the patients were women and their ages ranged from 28 to 73. Most of them were middle aged or postmenopause.

Dry mouth and dry eyes were present in all the patients and occasionally dryness of nose, throat, and skin. Deficient salivary secretion caused difficulty in swallowing solid food and mastication, and sometimes speaking. The tongue appeared dry, red, and smooth for the atrophy of the lingual papillae. The commissure of the lips was frequently the site of fissure and maceration. Almost all the patients had rapidly progressive dental caries.

Sialography of the parotid gland was undertaken on 19 patients. The sialogram manifested a variety of appearance because of the lack of normal secretion. Of these, 13 cases showed characteristic figures of sialectasis, and 4 cases revealed slight changes. Other 2 cases had a normal glandular structure as judged from the sialogram. Usually, the parotid duct was irregular and enlarged. The branches were tortuous and dilated, and terminated in small, rounded cavities. As the disease progressed, they showed typical appearance of sialectasis.

Table 2. Results of labial biopsies in twenty patients with Sjögren's syndrome

Case No.	Name	Cell infiltration	Germinal center	Ductal proliferation and dilatation	Epimyoepithelial Island	Atrophy of grandular tissue
1.	K.I.	++	−	+	−	+
2.	K.T.	+	−	−	−	−
3.	M.T.	+	−	+	−	+
4.	R.H.	++	−	+	−	++
5.	K.M.	+++	+	+	−	++
6.	C.T.	+	−	−	−	−
7.	A.E.	+++	−	+	−	+++
8.	T.M.	+++	−	+	±	+++
9.	S.T.	++	−	+	±	++
10.	S.I.	+++	−	+	+	+++
11.	Y.M.	+++	+	+	−	+++
12.	M.O.	++	−	+	−	+
13.	S.T.	++	−	+	−	+
14.	T.T.	+++	−	+	+	+++
15.	K.Y.	++	−	+	−	++
16.	R.S.	+	−	+	−	+
17.	K.K.	++	−	+	−	+
18.	S.T.	+	−	−	−	+
19.	M.I.	++	−	−	−	+
20.	M.T.	+	−	+	−	−

The Schirmer's test and Rose-Bengal staining were done at the Department of Ophthalmology of this University, and all the patients were regarded as abnormal.

Arthralgia or arthritis without definite swelling were noted in 15 cases, and Waaler Rose and latex fixation tests implied rheumatoid arthritis.

Biopsies were obtained from the lower lip of all patients. They showed a variable degree of lymphocytic infiltration and glandular atrophy, ranging form almost normal glandular tissue to complete parenchymal atrophy due to the replacement by lymphoid tissue as shown in Table 2. They were divided into three groups according to the degree of lymphocytic infiltration.

First group	+	slight infiltration	(Fig. 1)
Second group	++	moderate infiltration	(Fig. 3)
Third group	+++	severe infiltration	(Fig. 5,8)

First group: They showed, on the whole, almost normal glandular tissue but in some parts of the gland slight lymphocytic infiltration was found between acinar cells or around the small intralobular ducts. Some of the ducts were usually dilated.

Second group: Lymphocytic or mononuclear cell infiltration was noted

in this group and the secretory cells were beginning to disappear, replacing lobular architecture. Lymphocytic infiltration seemed to start from the circumference of the ducts and the ducts were often dilated or proliferated. Fibrous connective tissue was increased between acinar cells, but the atrophy of the glandular tissue was not remarkable yet in this group.

Third group: The glands showed severe parenchymal degeneration and atrophy by a heavy cellular infiltration by lymphocytes. Generally, the extent of acinar atrophy tended to parallel the lymphocytic infiltration. A massive infiltration of the lymphoid cells was noted in two cases, forming a germinal center (Fig. 6). In the final stage the ducts were encompassed by lymphocytes and formed epimyoepithelial island with the proliferation of ductal epithelium. Two epimyoepithelial islands were observed (Fig. 9), but the other two were not so characteristic.

Discussion

It is well known that the outstanding pathological feature of Sjögren's syndrome is the aggressive behavior of lymphoid cells, which infiltrate and destroy salivary and lacrimal glands.

Gougerot[8] first noted the association of xerostomia and keratoconjunctivitis with lymphocytic infiltration of the lacrimal glands. Morgan and Castleman[9,10] found that the histopathologic features of Mickulicz's disease and Sjögren's syndrome were indistinguishable.

In considering the histopathology of Sjögren's syndrome, there seem to be two impressive features to these lesions. The first one is the heavy infiltration of lymphoid cells into the glandular tissue and atrophy of the acini leading to a total substitution of the secretory parenchyma. The other property is the proliferation of epithelial lining of the excretory ducts to make dense islands of epithelial cells in a stroma of lymphatic tissue. According to Morgan and Castleman[9,10] the formation of epimyoepithelial island is a late feature of the disease process.

Recently the major and minor salivary glands in Sjögren's syndrome have been considered to represent the same characteristic histopathological appearances, and several investigators[5,11-15] have infrequently discussed the usefulness of minor salivary gland as the diagnostic aid in Sjögren's disease.

In 1966, Calman and Reifman[11] reported that the biopsy of cheek tissue would be of added value in making the diagnosis of Sjögren's syndrome. Cifarelli et al.[12] also showed that the minor salivary glands of a patient at the junction of the hard and soft palate represented an excellent and easily accessible biopsy site for the collaboration of Sjögren's syndrome.

Recently, Chisholm and Mason[13] have shown focal lymphocytic adenitis

of the labial salivary glands to be a consistent finding in patients with Sjögren's syndrome, although they were not able to demonstrate the typical appearance of Sjögren's syndrome with ductal proliferation and the formation of epimyoepithelial island. Bertram and Hjørting[14] reported that it was possible to find in 85% of his materials the characteristic histopathologic picture of salivary glands involvement in Sjögren's syndrome by a simple biopsy from labial salivary glands.

There are various biopsy sites in the minor salivary gland, such as the cheek, palate, or labial gland. Cifarelli[12] preferred biopsy of the palatal gland, but Bertram and Hjørting[14] did it from the labial gland. From our experiences, it is technically easier to obtain a salivary gland from the lip and there was no risk of bleeding.

From the results of our 20 cases, an approximate correlation was found between the severity of clinical symptoms and the extent of lymphocytic infiltration. The labial biopsy showed various degrees of histopathologic figures according to the disease process. The primary changes appeared to be an infiltration of the lymphoid cells around the intralobular small ducts and their dilatation. When the lymphocytic infiltration increased in the glandular tissue, the acinar cells began to disappear, and the ducts became more prominent. Then, the ductal epithelium proliferated. The degree of atrophy of acinar parenchyma seemed to parallel the extent of lymphocytic infiltration. We have observed the formation of a germinal center and epimyoepithelial island in 6 cases, which is the most characteristic figures in Sjögren's syndrome. These cases have shown severe clinical symptoms and remarkable radiological evidence of sialectasis in the parotid gland. However, according to Chisholm et al.[15], the severity of sialographic abnormality did not always express a decrease in parotid gland function.

According to Schall et al.[16,17], there was no correlation between the scintigraphic classification and lip biopsy results. They said that, in almost all cases, the histopathology suggested a more serious disease than was apparent from the function. However, from our clinical results, the severity of histopathologic features of lip biopsy seemed to some extent to parallel the changes of the parotid sialogram and other clinical symptoms but, as we have not examined the salivary flow rate in this study, we cannot discuss the problem of the function with the result of biopsies and sialograms.

The relation of Sjögren's syndrome to rheumatoid arthritis and other connective tissue diseases has been the subject of a great deal of discussion in the literature. From the results of postmortem prevalence of focal lymphocytic adenitis of the submandibular salivary gland, Waterhouse and Doniach[18] recognized a strong evidence for the association between focal sialadenitis and rheumatoid arthritis, and they have suggested that these changes may

represent a potential rheumatoid state in these subject. Chisholm and Mason[13] also found that the patient with rheumatoid arthritis alone also had lymphocytic focus in the minor salivary gland. As rheumatoid arthritis occurs in about three-fourths of our cases, it is difficult to dismiss the association as mere coincidence. The focal sialadenitis, at any site, does not represent the changes of Sjögren's syndrome alone. It may suggest that the lymphocytic focus is an epiphenomenon of rheumatoid arthritis rather than a manifestation of Sjögren's syndrome. More recently, utilizing biopsy specimens from the lower lip, Anderson et al.[19] have found the local synthesis of a large amount of immunoglobulins (IgM and IgG) and rheumatoid factor in salivary glandular tissue in Sjögren's syndrome.

According to these evidences, it may be true that the lymphocytic infiltration is a morphological pointer for the general disturbance of immunological system that leads to an auto-immune disease.

However, the fact that there has been a significant degree of correlation between lymphocytic infiltration of the labial salivary gland and clinical symptoms in Sjögren's syndrome would be a valuable diagnostic aid, if we consider the results with other clinical findings.

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Explanation of Figures

Plate 1

Fig. 1. Slight lymphocytic infiltration in the glandular tissue (Case No. 6). ×110.
Fig. 2. Sialogram of almost normal parotid gland (Case No. 6).

Plate 2

Fig. 3. Moderate lymphocytic infiltration in the glandular tissue (Case No. 4). ×150.
Fig. 4. Sialogram showing moderately changed sialectasis (Case No. 4).

Plate 3

Fig. 5. Severe lymphocytic infiltration, forming a germinal center (Case No. 5). ×60.
Fig. 6. Higher magnification of germinal center (Case No. 5). ×150.
Fig. 7. Sialogram showing severe change of sialectasis. The terminal duct radicals had berry-like dilatation (Case No. 5).

Plate 4

Fig. 8. Severe lymphocytic infiltration with the proliferation of ductal epithelium and epimyoepithelial island (Case No. 10). ×60.
Fig. 9. Higher magnification of the epimyoepithelial island (Case No. 10). ×150.
Fig. 10. Sialogram showing advanced change of sialectasis and main duct dilatation (Case No. 10).

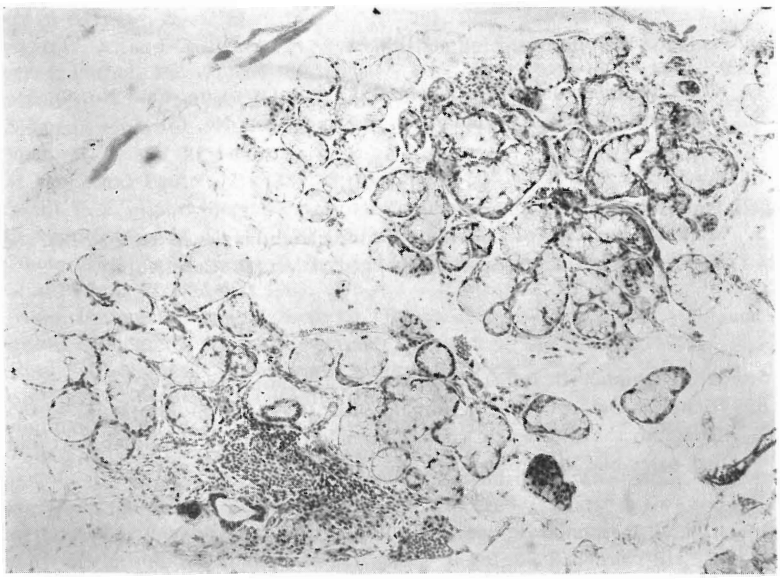


Fig. 1.

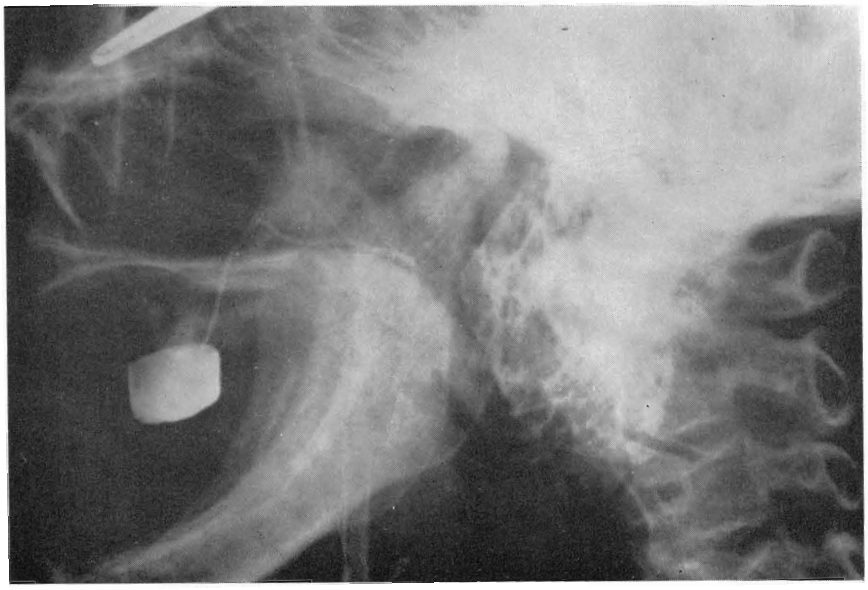
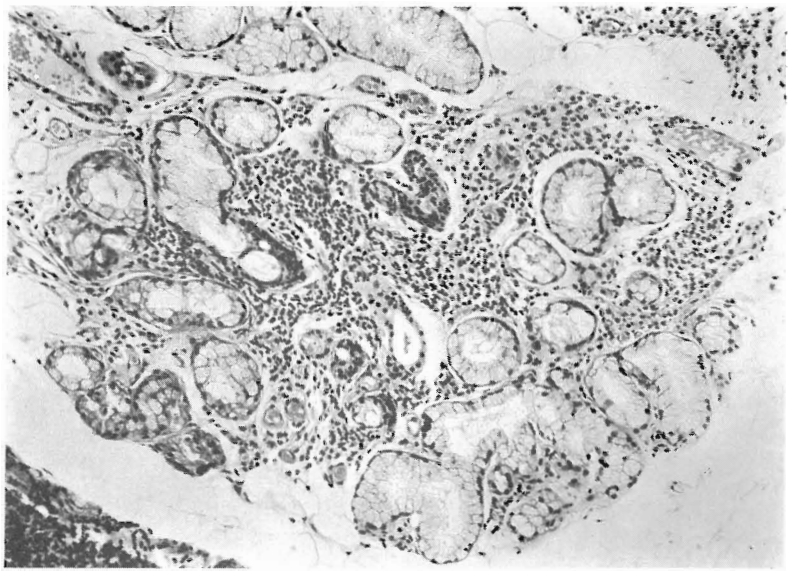


Fig. 2.



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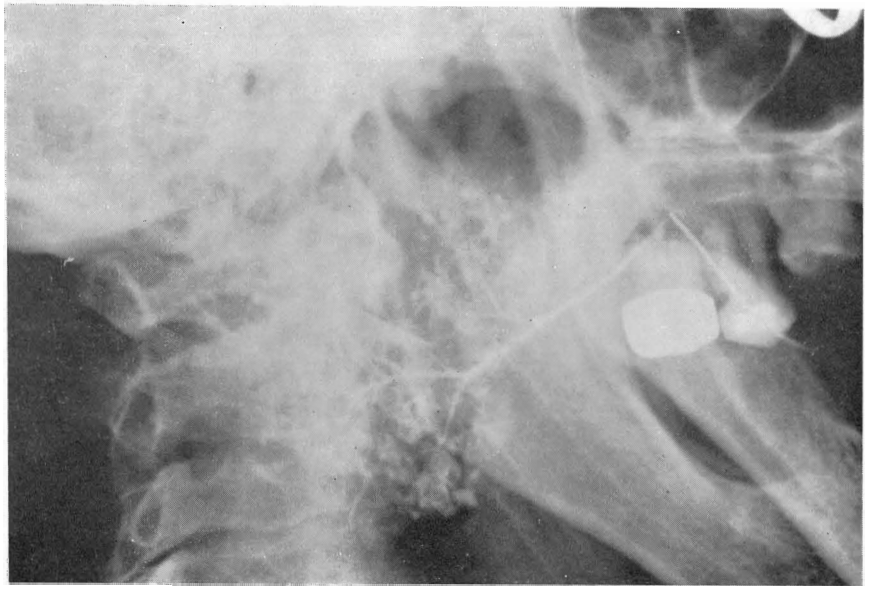

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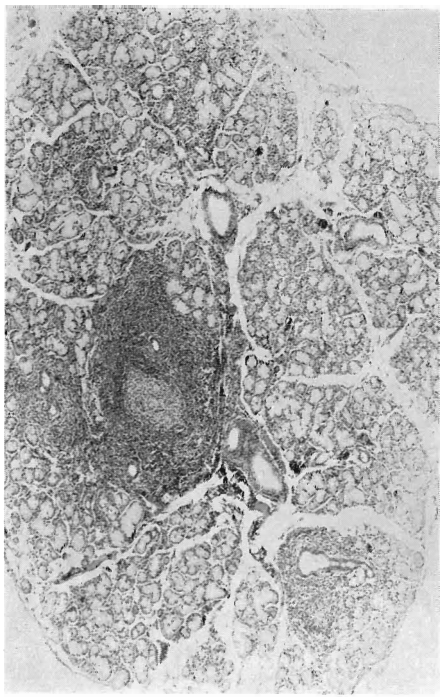

Fig. 5.

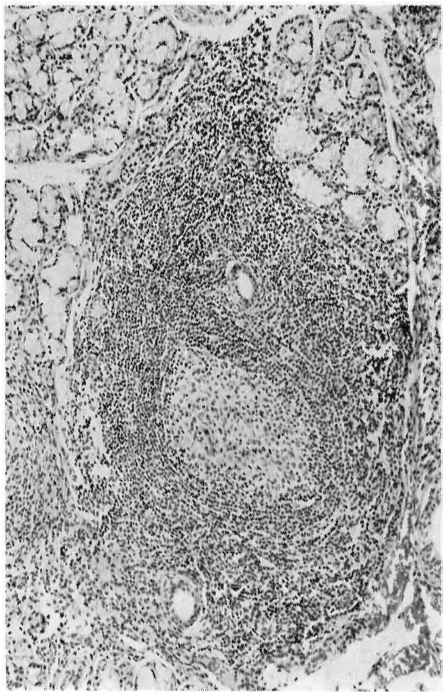

Fig. 6.

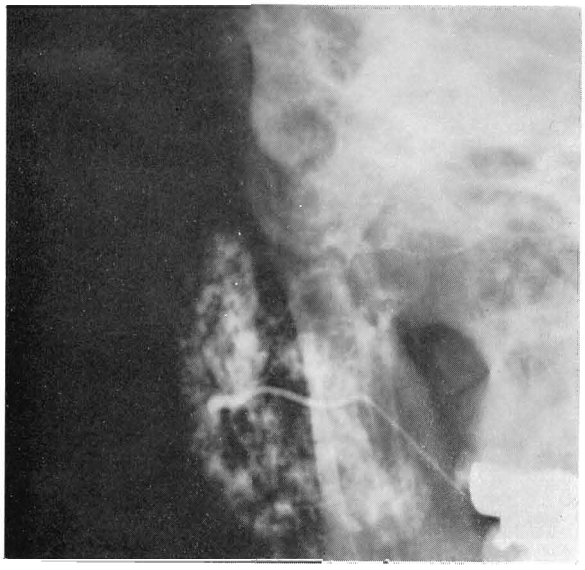

Fig. 7.

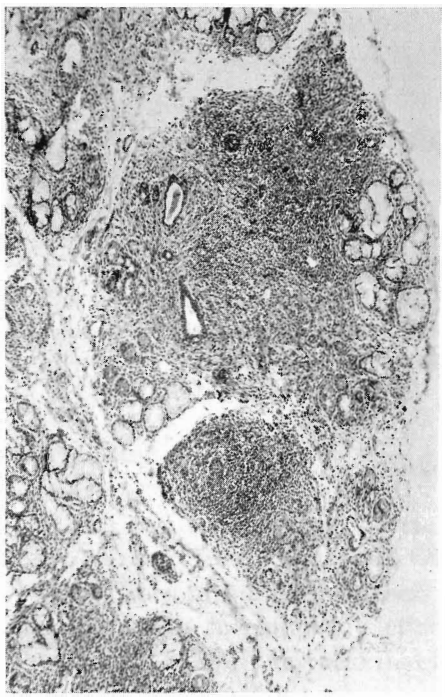

Fig. 8.

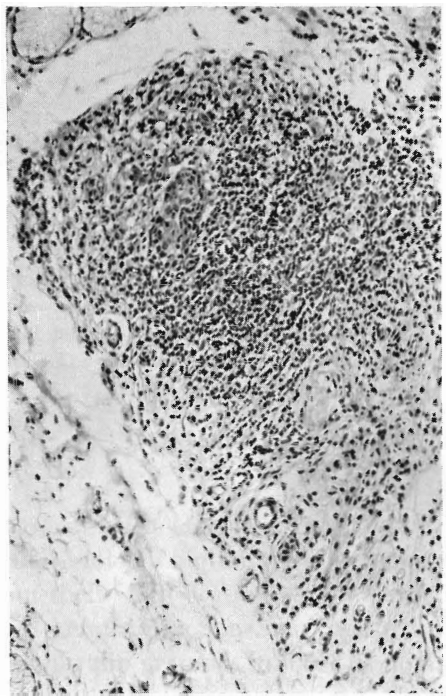

Fig. 9.

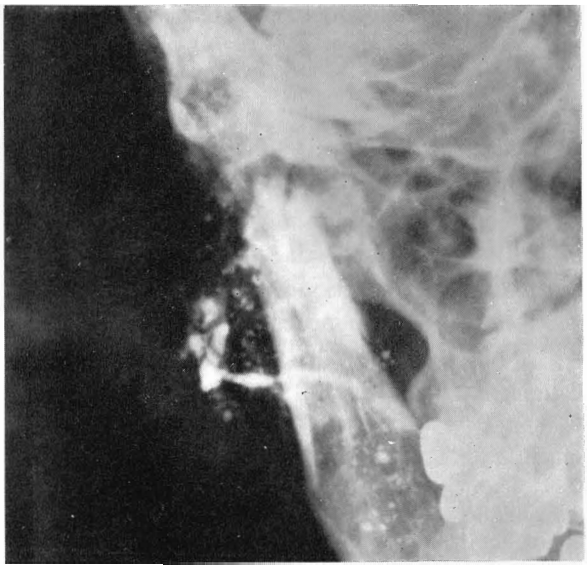

Fig. 10.