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HISTOLOGICAL OBSERVATION OF THE SUBMANDIBULAR GLAND WITH SPECIAL REFERENCE TO THE FOCAL LYMPHOCYTIC INFILTRATION

BY

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ABSTRACT

Focal lymphocytic infiltration of the submandibular gland was investigated on the autopsy cases. The materials examined were 340 cases without the collagen diseases and 28 cases with collagen diseases. Of the 28 cases with collagen diseases, 20 were systemic lupus erythematosus, 2 with the coexistence of systemic lupus erythematosus and Sjögren's syndrome, 4 with rheumatoid arthritis and 2 with progressive systemic sclerosis. Among the cases without the collagen diseases, the focal lymphocytic infiltration was seen in 154 cases (74%) of 209 males and in 94 cases (71%) of 131 females. All 28 cases with collagen diseases had a focal lymphocytic infiltration. The incidence of grade 3 or severe infiltration was 4% in the males and 14% in the females in the cases without the collagen diseases, 65% in the 20 cases with systemic lupus erythematosus, 50% in the 4 cases with rheumatoid arthritis and 50% in the 2 cases with progressive systemic sclerosis. No cases of very severe infiltration were found, which were seen in the classical Sjögren's syndrome, in both cases with and without the collagen diseases. Hyperplastic change in the ductal cells, which can be called an epimyoepithelial island, was found in 23% of the cases with collagen diseases. These observations suggest that the focal lymphocytic infiltration is a focal sign of the immunologic disorder of the submandibular gland in the collagen disease.

INTRODUCTION

It is well known that the focal lymphocytic infiltration frequently occurs in the submandibular gland (Waterhouse and Doniach [1], Scott [2]). Waterhouse and Doniach [1] examined the prevalence of focal lymphocytic sialadenitis of the submandibular glands and stated that the severer grade of infiltration was found in the 35–64-year group in the female and focal lymphocytic sialadenitis had an association with the collagen diseases such as rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa and scleroderma. Alarcon-Segovia et al [3] described about the high rate of the involvement of the coexistence of Sjögren's syndrome and systemic lupus erythematosus. The coexistence of Sjögren's syndrome and collagen diseases has been reported by many other authors (Bloch et al [4], Shearn [5], Steinberg and Talal [6], Gahagan [7], Bencze and Lakatos [8], Bain [9] and Grennan and Buchanan [10]).

The present paper reports on the prevalence of the focal lymphocytic infiltration in the submandibular glands taken from 368 necroscopied patients with and without the collagen diseases. The significance of the infiltraton of the submandibular glands in the collagen diseases was discused.

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Materials and Methods

Three hundred and sixty-eight submandibular glands were obtained from autopsies carried out at the Tokyo Medical and Dental University and several other hospitals from 1965 to 1980. Three hundred and forty cases had not been affected with any collagen disease or autoimmune disease, leukemia, malignant lymphoma, tumors of the head and neck, and local infectious diseases.

There were 28 cases with collagen diseases, consisting of 22 cases of systemic lupus erythematosus, 4 cases of rheumatoid arthritis and 2 cases of progressive systemic sclerosis. The diagnosis of the collagen diseases had been confirmed by clinical findings and autopsy examinations. Two cases had systemic lupus erythematosus coexisting with the classical features of Sjögren's syndrome. Five patients with systemic lupus erythematosus had oral and symptoms although the clinical diagnosis of Sjögren's syndrome had not been obtained. All patients with collagen diseases had received a long-term corticosteroid therapy.

The submandibular glands collected by autopsies were fixed in 10% formalin and cut in to three slices. The sections were stained with hematoxylin and eosin. The maximal area among the three sections was measured by the use of image analyzing computer (Quantiment-720), by which the number of ficu consisting of lymphocytes and plasma cells was counted. The grading of the degree of lymphoplasmocytic infiltration was followed by Waterhouse and Doniach [1].

For the electron microscopical study, the tissues were cut into 1 mm^3 or smaller sections in ice-cold 2.5% glutaraldehyde phosphate buffer (pH 7.4), then rinsed several times in 0.1 M phosphate buffer (ph 7.4) and kept overnight. Following post-fixation with 2% osmic acid for two hours, they were dehydrated in graded ethanol, treated with propylene oxide and embedded in Epon 812. The ultrathin sections for electron microscopy were double-stained with uranyl acetate and lead citrate. These sections were observed by the Hitachi HU-12 microscopy.

Result

I. *Cases without collagen diseases*

The relationship between the grade of the focal lymphocytic infiltration and the age, sex and basic diseases is shown in Tables 1, 2 and 3. Focal lymphocytic

Table 1. Incidence of Focal Lymphocytic Infiltration in Male Patients Without Collagen Diseases

Age in years	Grade of severity					Total	Per cent positive
	0	1	2	3	4		
0–19	6	3	8	1	0	18	67%
20–29	4	5	9	0	0	18	78%
30–39	8	6	6	2	0	22	64%
40–49	3	7	7	0	0	17	82%
50–59	12	12	12	0	0	36	67%
60–69	14	19	12	2	0	47	70%
70–79	6	13	17	1	0	37	84%
Over 80	2	8	2	2	0	14	86%
Total	55	73	73	8	0	209	74%
Per cent positive	26%	35%	35%	4%	0	100%	

Table 2. Incidence of Focal Lymphocytic Infiltration in Female Patients Without Collagen Diseases

Age in years	Grade of severity					Total	Per cent positive
	0	1	2	3	4		
0–19	9	2	3	2	0	16	44%
20–29	1	3	1	0	0	5	80%
30–39	2	0	3	4	0	9	78%
40–49	5	6	8	4	0	23	78%
50–59	10	9	7	1	0	27	63%
60–69	5	9	12	5	0	31	84%
70–79	6	6	3	2	0	17	65%
Over 80	0	1	2	0	0	3	100%
Total	38	36	39	18	0	131	71%
Per cent positive	29%	27%	30%	14%	0	100%	

Table 3. Incidence of Focal Lymphocytic Infiltration in Relation to basic Diseases

Disease	Grade of severity					Total	Per cent positive
	0	1	2	3	4		
Tumor	63	69	56	11	0	198	68%
Diseases of heart & blood vessels	5	17	20	1	0	43	88%
Hepatic disease	4	6	5	3	0	18	82%
Diseases of nervous system	5	2	4	6	0	17	71%
Renal diseases	0	4	9	2	0	15	100%
Pulmonary diseases	2	3	8	1	0	14	86%
Blood diseases	0	3	2	1	0	6	100%
Diabetes mellitus	1	0	2	1	0	4	75%
Anomalies and stillbirths	11	0	1	0	0	12	8%
Others	2	5	6	0	0	13	85%
Total	93	109	112	26	0	340	73%
Per cent positive	27%	32%	33%	8%		100%	

infiltration was seen in 74% of the males and 71% of the females. The prevalence of the focal lymphocytic infiltration was lower in the age group under 20 years. The frequency of grade 3 or severe focal lymphocytic infiltration was 4% in the males and 14% in the females. Grade 4 or very severe infiltration was not found in any case. Histologically, infiltration occurred usually in the periductal and perivascular areas of the lobules and between the lobules and the cells were composed mainly of lymphocytes, and the number of plasma cells was few (Fig. 1). There was seen hyperplasia of the ductal epithelium, which could be called an epimyoepithelial island, in 4 cases and the hyperplastic change was accompanied by a severe grade of lymphocytic infiltration (Fig. 2). A follicular structure with a germinal center was seen in only one case, a 2.5-year-old child with sepsis. In 21 cases with renal and blood diseases, the focal lymphocytic infiltration was

seen in all cases. In 11 cases with anomaly and stillbirth, only one child with the Pierre Robin syndrome showed infiltration.

II. *Cases with systemic lupus erythematosus alone*

The clinical summary of the 22 cases with systemic lupus erythematosus with and without Sjögren's syndrome is shown in Table 4. The grade of the focal lymphocytic infiltration and other histologic changes in the submandibular glands are summarized in Table 5. Focal lymphocytic infiltration was found in all 20 glands. The cell infiltration consisted predominantly of mature lymphocytes, and few plasma cells were present. Grade 3 or severe lymphocytic infiltration was seen in 13 cases (63%), and grade 2 or moderate lymphocytic infiltration was seen in 5 cases (25%). Slight lymphocytic infiltration was in 3 cases. There were no cases of grade 4 lymphocytic infiltration. In the submandibular glands with severe lymphocytic infiltration, atrophy or diminution of the acinar cells was seen (Fig. 3). Formation of the germinal centers was not observed in all cases. Hyperplasia of the duct cells were observed in 11 cases (55%) and 4 of them could be called epimyoepithelial islands (Fig. 4). Homogenous eosinophilic material was occasionally present in these islands. Oncocytic change in the ductal epithelium was seen in 17 cases.

III. *Cases with coexistence of systemic lupus erythematosus and Sjögren's syndrome*

The clinical summary is shown as case numbers 21 and 22 in Table 4. The parenchyma of the submandibular glands

Table 4. Clinical Summary of 22 Cases With Systemic Lupus Erythematosus

Case	Age (yrs.)	Sex	Duration of illness	Cause of Death	Sicca Symptoms and other complications
1	14	F.	4 y. 10 m.	Uremia	Parotitis at age of 9
2	35	F.	2 y. 2 m.	Uremia	Not described
3	18	F.	2 m.	Uremia	Not described
4	14	M.	2 y.	Uremia	Not described
5	43	F.	6 y.	Pyelonephritis	Enlargement of paroid gland
6	28	F.	5 y. 6 m.	Pulmonary edema	Not described
7	22	F.	5 y.	Uremia & DIC	Xerostomia
8	26	M.	2 y. 3 m.	Uremia	Cryptococcosis
9	19	F.	7 y.	Uremia	Tuberculous pyelonephritis
10	31	F.	2 y.	Bronchopneumonia	Not described
11	35	F.	1 y. 7 m.	Miliary tuberculosis	Drug eruption (Lyell)
12	42	F.	22 y.	Pulmonary embolism	TTP
13	36	F.	8 y. 5 m.	Uremia	Not described
14	27	M.	10 y.	Bronchopneumonia	Not described
15	32	F.	8 y.	Respiratory disturbance	Dimness of eye Primary pulmonary hypertension Hashimoto's disease
16	29	F.	10 y.	Subarachnoidal hemorrhage	Decreased volume of saliva by Gum test
17	29	F.	5 y.	Uremia	ITP
18	40	F.	15 y.	Hemorrhagic diathesis	Not described
19	32	F.	10 y.	Uremia	Hypertension
20	28	F.	8 y.	Uremia	Not described
21	45	F.	9 y.	Acute purulent mediastinitis	Sjögren's syndrome Gastric carcinoma
22	35	F.	13 y.	Systemic fungal infection	Sjögren's syndrome

Table 5. Microscopical Findings of Cases With Systemic Lupus Erythematosus

Case	Extent of infiltration of lymphocytes	Reduction of secretory parenchyma	Hyperplastic duct change	Epimyo-epithelial island	Oncocytic change	Fat infiltration
1	3	++	+	−	−	−
2	1	−	−	−	−	+
3	3	++	+	−	+	+
4	3	++	+	+	−	+
5	3	++	+	−	+	+
6	3	++	−	−	+	−
7	3	++	+	−	+	−
8	2	+	−	−	+	−
9	2	+	−	−	+	+
10	2	+	−	−	+	+
11	3	++	−	−	+	+
12	2	+	−	−	+	+
13	3	++	−	−	−	++
14	1	−	+	−	−	−
15	3	++	−	−	+	−
16	2	+	−	−	+	+
17	3	++	++	++	++	−
18	3	++	+	−	+	+
19	3	++	+	+	+	+
20	3	++	+	−	+	++

in 2 cases was replaced widely by the fibro-adipose tissues (Fig. 5). The remaining parenchyma showed a marked atrophy. In both cases, there were moderate lymphocytic infiltration, ductal proliferation, occasional formation of the epimyoepithelial islands and an oncocytic change in the ductal epithelium.

IV. *Cases with other collagen diseases*

The clinical summaries of the 6 cases of rheumatoid arthritis and progressive systemic sclerosis are shown in Table 6. The severity of the focal lymphocytic infiltration and other findings of the submandibular glands are summarized in Table 7. All these cases showed a focal lymphocytic infiltration with an occasional formation of epimyoepithelial islands and deposition of hyaline substance (Fig. 6). The germinal center was not found in all cases.

V. *Electron microscopic findings*

Electron microscopic examinations were done on 6 cases of systemic lupus erythematosus, one case of systemic lupus erythematosus with coexisting Sjögren's syndrome and one case of rheumatoid arthritis. Cellular infiltrates consisted of a large number of small lymhocytes, and mature plasma cell and macrophages were not plentiful (Fig. 7). The epimyoepithelial islands were observed in one case of rheumatoid arthritis. The islands were surrounded by the basal lamina of 50–100 nm-thickness and consisted of the proliferation of the ductal cells and epimyoepithelial cells. Occasionally, deposition of the electron-dense materials was seen in the intercellular spaces (Fig. 8). The ductal cells were joined by well-developed desmosomes and contained a large amount of tonofilaments in the cytoplasm (Fig. 9). Intercellular electron-dense material contained basement membrane-like materials, collagen filaments and fibrils and communicated with the connective tissue outside the island. There was a small

Table 6. Clinical Summary of Cases With Rheumatoid Arthritis (RA) and Progressive Systemic Sclerosis (PSS)

Case	Age (yrs.)	Sex	Duration of illness	Collagen disease	Cause of death	Other complications
1	51	M.	6 y.	RA	Sepsis	Polyarteritis nodosa
2	47	F.	2 y. 7 m.	RA	Heart failure	Carcinoma of the tongue
3	28	F.	15 y.	RA	Pulmonary fibrosis	Pulmonary fibrosis
4	54	F.	15 y.	RA	Acute bronchopneumonia	Osteoporosis
5	44	F.	1 y. 8 m.	PSS	Heart failure	Polymyositis
6	41	F.	5 y.	PSS	Heart failure	Carcinoma of the cervix

Table 7. Microscopical Findings of Cases With Rheumatoid Arthritis and Progressive Systemic Sclerosis

Case	Extent of infiltration of lymphocytes	Reduction of secretory parenchyma	Hyperplastic duct change	Epimyo-epithelial island	Oncocytic change	Fat infiltration
1	3	++	+	+	−	++
2	2	+	−	−	+	+
3	3	+	++	++	+	+
4	1	−	−	−	−	+
5	3	+	+	+	−	++
6	2	+	−	−	−	+

number of lymphocytes in the islands. Microtubular structures were demonstrated in the cytoplasma of the endothelium in the cases with the coexistence of systemic lupus erythematosus and Sjögren's syndrome (Fig. 10).

Discussion

The present study was made on the incidence of the focal lymphocytic infiltration of the submandibular glands in 340 cases without the collagen diseases and 28 cases with collagen diseases. In 340 cases without the collagen diseases the incidence was 74% in the males and 71% in the females. This shows a relatively high incidence of focal lymphocytic infiltration of the submandibular glands, even in the cases without the collagen disease. However, generally the degree of the severity was more slight in the cases without the collagen diseases. Among the cases without the collagen diseases with grade 3 or severe infiltration, there was seen a sexual difference in the ration of the females to the males: 14%:4%. It may be possible that this difference is related to the higher tendency for the females to be affected by the collagen diseases, (Dubois [11]).

Focal lymphocytic infiltration of the submandibular glands with systemic lupus erythematosus was very common and it was seen in all the glands examined. The grade of the focal lymphocytic infiltration was moderate to severe in 18 cases and slight in 2 cases. The proliferation of the ductal epithelium was found in 10 cases and 3 of them showed a formation of epimyoepithelial islands. Five of 20 cases with systemic lupus erythematosus alone had xerostomia and 4 of them disclosed a severe degree of lymphocytic infiltration. These observations revealed that the histologic changes as seen in Sjögren's syndrome can occur in the submandibular glands of the patients with systemic lupus erythematosus.

The overlapping syndrome may suggest an intimate relationship between the systemic lupus erythematosus and Sjögren's syndrome. However, it is imperative to clarify further whether the focal lymphocytic infiltration of the submandibular glands with or without the formation of the epimyoepithelial islands may indicate the presence of the subclinical Sjögren's syndrome or whether the infiltration is another immunological phenomenon related to the pathogenesis of systemic lupus erythematosus. Alarcon-Segovia et al [3] indicated that the clinical manifestation or subclinical evidence of Sjögren's syndrome could be found in almost all 50 patients with systemic lupus erythematosus, and Grennan and Buchanan [10] also described the same results. Morgan and Castleman [12] described about the frequent involvement of the lymphocytic infiltration of the salivary glands in the patients with systemic lupus erythematosus.

The submandibular glands of the patients coexisting with Sjögren's syndrome, at the time of autospy, were replaced by the fatty tissue, and the lymphocytic infiltration was slight with the formation of the epimyoepithelial islands. However, judging from the observation on the biopsy of the parotid gland, probably the submandibular glands has also been infiltrated severely by the lymphocytic cells. The microscopic features of the salivary gland of the collagen disease might be largely modified by the long-term administration of corticosteroid.

Grade 3 or severe focal lymphocytic infiltration with the formation of epimyoepithelial islands was seen in 2 cases of rheumatoid arthritis and one case of progressive systemic sclerosis. There could not be found any significant difference in the microscopic features of the submandibular glands among the case of systemic lupus erythematosus, rheumatoid arthritis and progressive systemic sclerosis. This, also, might be meaningfully indicative of the relationship of rheumatoid arthritis and progressive systemic sclerosis to Sjögren's syndrome. The coexistence of rheumatoid arthritis and Sjögren's syndrome has been reported by many authors (Bloch and Buchanan [4], Shearn [5] and Bencze and Lokatos [8]). Alarcon-Segovia et al [13] noted that all 25 patients with progressive systemic sclerosis had at least one abnormal finding by the many laboratory tests for the diagnosis of Sjögren's syndrome.

Rauch and Gorlin [14] described that the epithelial ductal hyperplasia is missing in collagen sialadenitis and they considered that the epimyoepithelial islands are specific for Sjögren's syndrome. However, in the present study, epimyoepithelial islands were seen in the cases with systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis and even in the cases without the collagen diseases. And so it is considered that the formation of the epimyoepithelial islands is not pathognomonic for Sjögren's syndrome.

Electron microscopically, the focal lymphocytic infiltrates consisted manily of mature lymphocytes and the palsma cell were not plentiful. The lymphocytes infiltrated into the interlobular and intralobular periductal spaces. Occasinally they were present in the epimyoepithelial islands. The epimyoepithelial islands consisted of the myoepithelial and ductal cells, and the tonofilaments were relatively rich in the cytoplasma of the ductal cells which were joined by the well-developed desmosomes. These changes resembled the squamous metaplasia of the ductal cells (Komori et al

[15]). The hyaline material seen by light microscopy contained a basement membrane-like substance and collagen filaments and fibrils. Immunoglobulins A, G and M were positively stained but it is yet inconclusive whether the hyaline substance contained immunogloblin, because by the author's immunohistochemistry study, the surrounding collagen fibers of the islands were also stained.

In conclusion, the exact meaning of the focal lymphocytic infiltration of the submandibular glands has not been fully understood, but the high incidence of the severe lymphocytic infiltration in the collagen diseases might suggest the possibility that it is a focal sign of the immunologic disorders in the submandibular glands of the patients affected by the collagen diseases. Moreover, although the true relationship between Sjögren's syndrome and the other collagen diseases is not yet known, from the same microscopic features among these lesions one can also suppose that there is a common etiologic factor in the pathogenesis of these lesions.

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LEGENDS TO THE FIGURES

Fig. 1. Grade 3 or severe focal lymphocytic infiltration seen in the periductal portion in the case with pulmonary tuberculosis. Hematoxylin and eosin, ×230.

Fig. 2. Epimyoepithelial island with focal lymphocytic infiltration in the case with diabetes mellitus. Hematoxylin and eosin, ×260.

Fig. 3. Severe lymphocytic infiltration with atrophy of the acinar cells seen in the case with systemic lupus erythematosus. Hematoxylin and eosin, ×170.

Fig. 4. Hyperplastic change in the duct with lymphocytic infiltration seen in the case with systemic lupus erythematosus. Hematoxylin and eosin, ×230.

Fig. 5. Marked atrophy of the parenchyma replaced by the fibro-adipose tissue, epimyoepithelial island and lymphocytic infiltration seen in the case with the coexistence of systemic lupus erythematosus and Sjögren's syndrome. Hematoxylin and eosin, ×65.

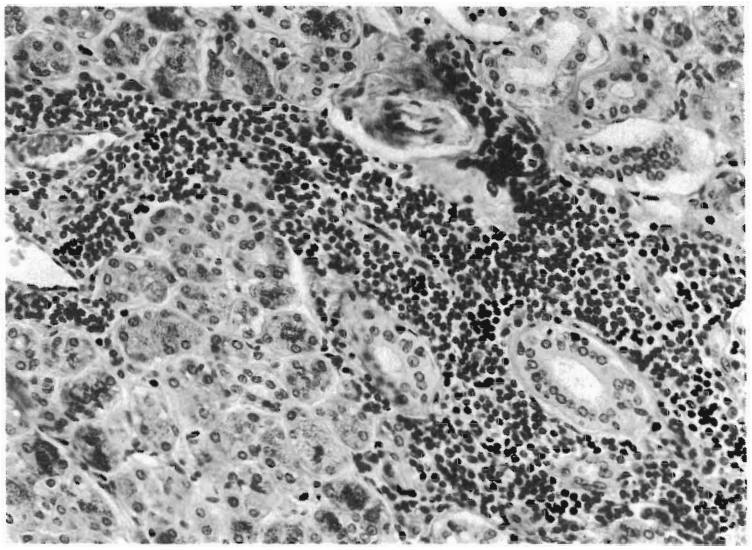
Fig. 6. Hyperplastic change of the duct and deposition of hyaline material seen in the case with rheumatoid arthritis. Hematoxylin and eosin, ×210.

Fig. 7. Cellular infiltrate consisting mostly of small lymphocytes in the case with systemic lupus erythematosus. ×2,880.

Fig. 8. Epimyoepithelial island consisting of ductal cells and myoepithelial cells. Electron-dense material and a few lymphocytes are seen in the island. Case with rheumatoid arthritis. ×1,920.

Fig. 9. The ductal cells in the epimyoepithelial island have abundant tonofilaments in the cytoplasm and are joined by the desmosomes. Case with rheumatoid arthritis. ×12,000.

Fig. 10. Microtubular structures seen in the endothelium in the case with the coexistence of systemic lupus erythematosus and Sjögren's syndrome. ×33,600.



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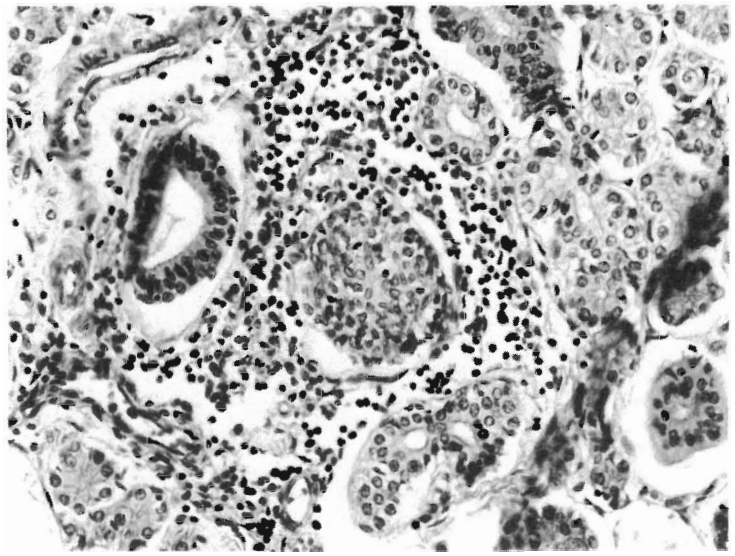

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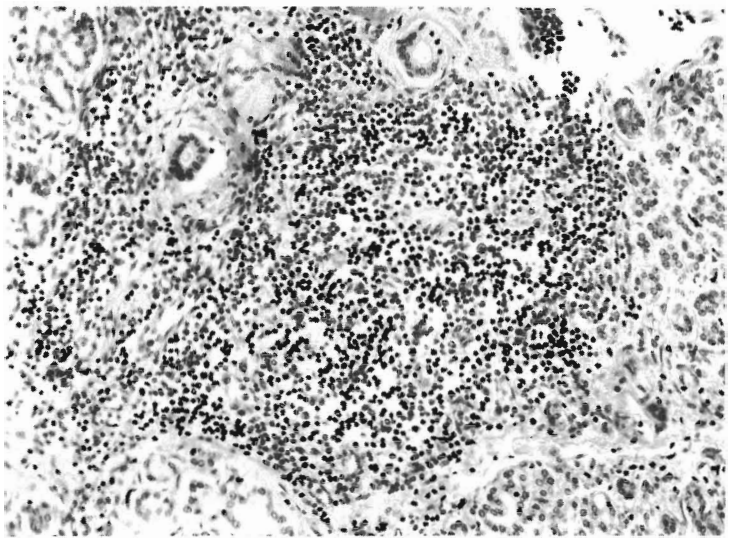

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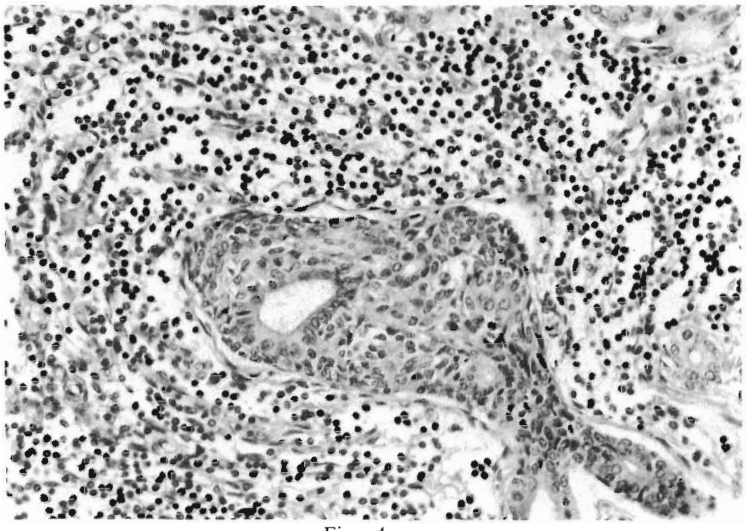

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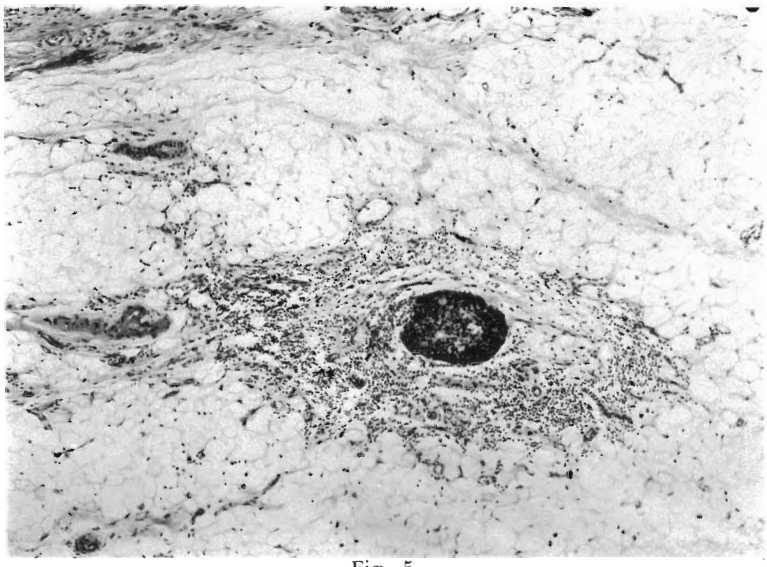


Fig. 5.

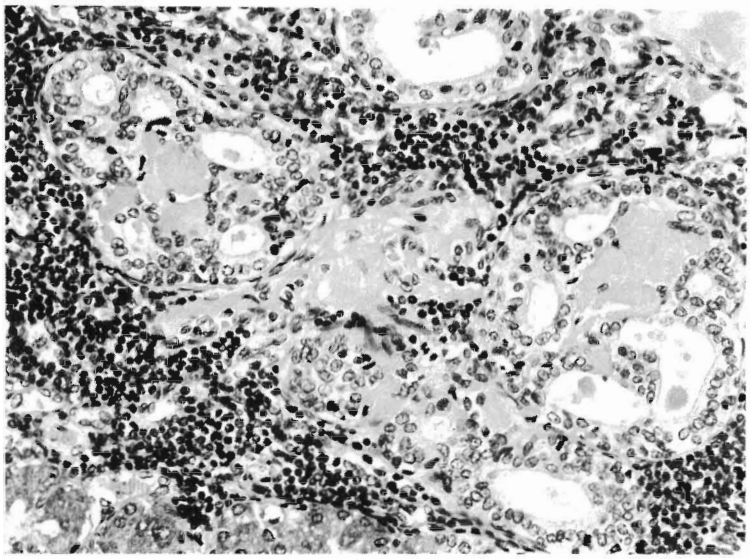


Fig. 6.

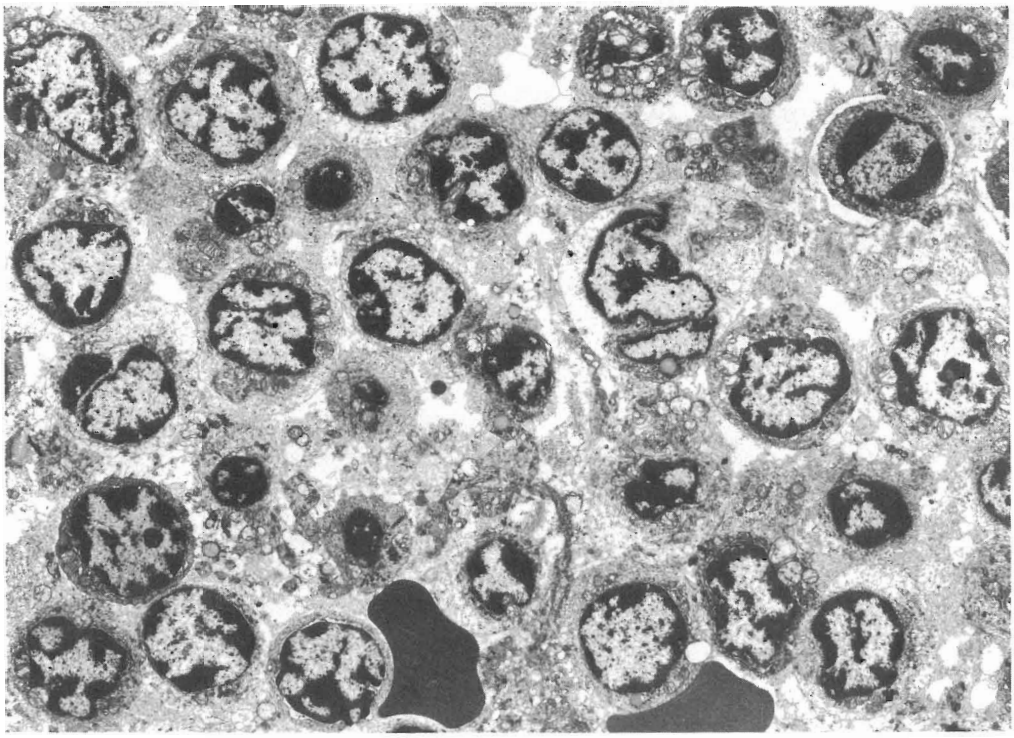
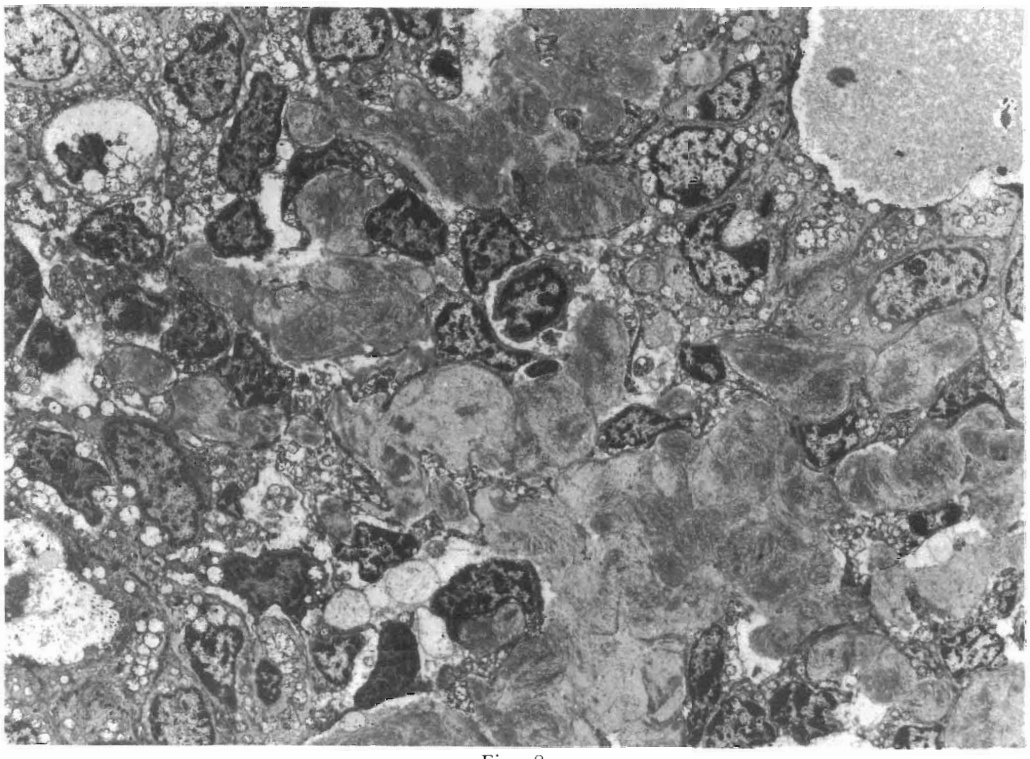


Fig. 7.



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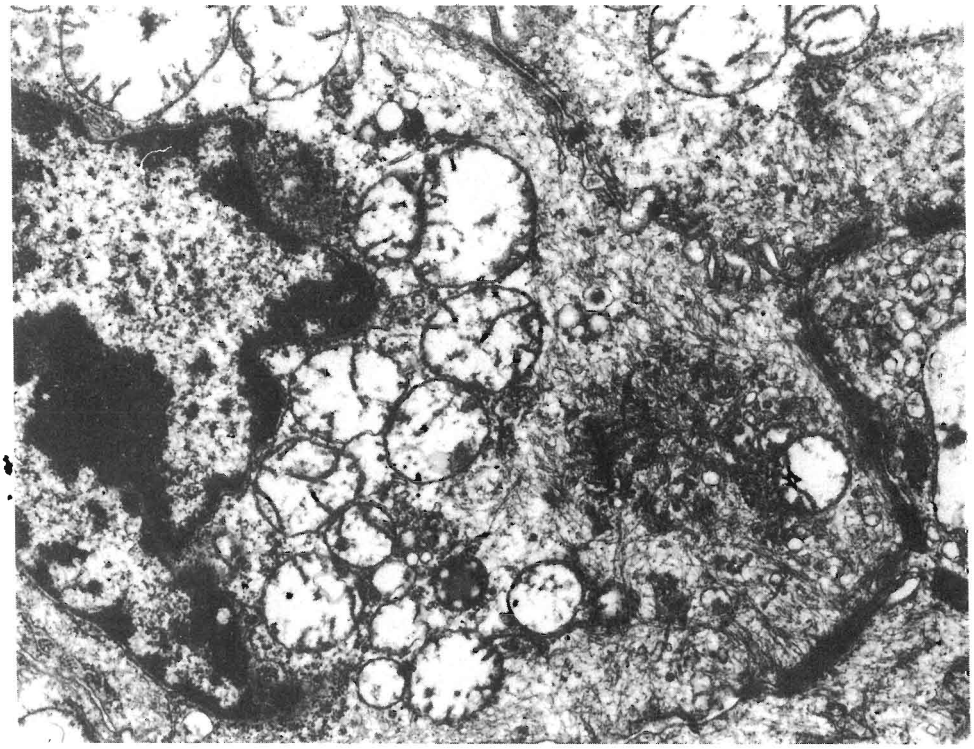

Fig. 9.

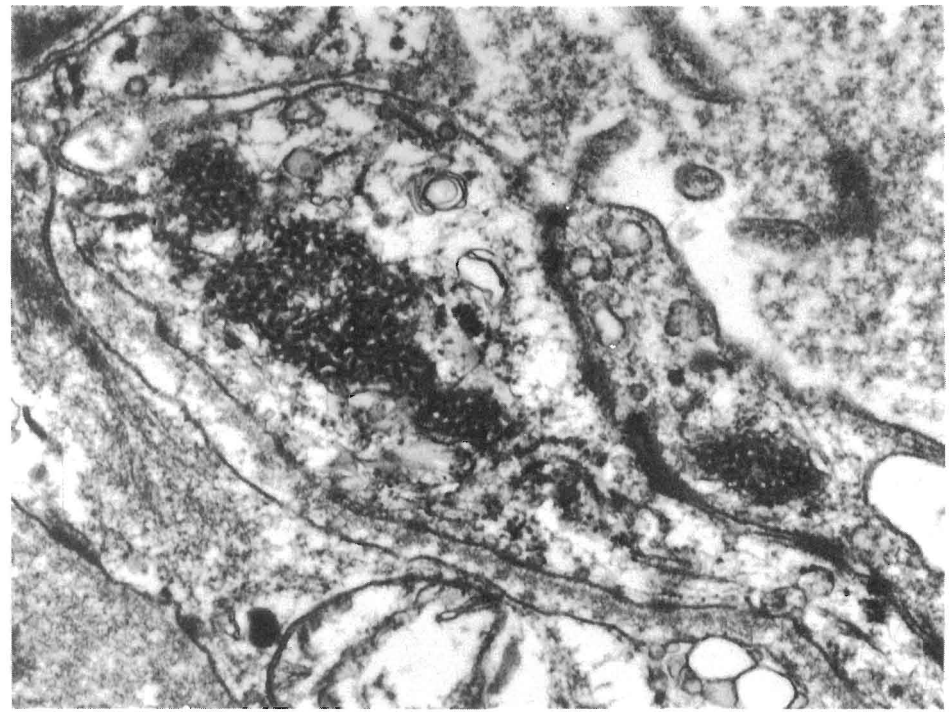

Fig. 10.