A CLINICOPATHOLOGIC STUDY OF "MIKULICZ'S DISEASE" *

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In 1888, Johann Mikulicz described at a meeting of the Society for Scientific Medicine in Königsberg the disease, later to bear his name, characterized by bilateral, chronic, painless hypertrophy of the lacrymal and salivary glands. The original case was that of a 42-year-old man in whom, over a period of 7 months, swelling of the lacrymal glands appeared first, followed by swelling in the submaxillary and parotid regions. After removal of two thirds of the lacrymal tumors, swelling reappeared in about 2 months. Further excision of the remaining portions of the lacrymal tumors and the submaxillary glands resulted in improvement, although swelling of the parotid glands persisted. The patient died several months later of probable peritonitis, at which time the swellings were markedly decreased in size.

Mikulicz's paper was published 4 years later.[1] The gross and microscopic features are brought out in the following translated excerpts.[1a]

"The submaxillary glands which had been removed in toto are most deserving of consideration. First of all it must be brought out that each of the glands, swollen to the size of a child's fist, corresponded exactly in relation to form and segmentation into lobes and lobules to the proportions of the normal gland. . . . The tumor shows, in its gross microscopic details, the normal structure of the gland, only it is increased in mass. An essential difference is found, however, by the naked eye in the fresh transverse section in the color and finer structure of the glandular mass forming the individual lobules. In place of the finely granular, gray red structure of the normal gland substance, we see a more homogenous, pale reddish yellow, amyloid mass of lesser transparency. Its consistency is decreased and very fatty. . . .

"The microscopic examination revealed that the main mass of the tumor was a pretty uniformly arranged tissue consisting of small round cells. . . . Here and there the cells lay compactly together; in other places a fine reticulum is to be seen between them. In single, large cells karyokinetic figures can be recognized. Imbedded in these small-celled main masses there appear, partly single and partly in groups, the apparently unchanged acini of the salivary gland; they are separated from one another in varying distances by the round cell tissue.

"Similar relations present themselves in the microscopic examination of the lacrymal gland; only here the acini were found less frequently and, it seemed, were entirely lacking in the outer compressed part of the tumor."

On the basis of the benign course manifested by the patient without evident involvement of the general lymphatic system, subsequent regression of the tumor masses, and on the gross and microscopic findings, Mikulicz concluded that the condition was one of a chronic

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low-grade infection. He refused to accept as additional examples of the disease, several cases showing similar bilateral enlargement of the lacrymal and salivary glands, proved to be malignant lymphoma, tuberculosis, and acute inflammation, maintaining that its etiology was of a more obscure nature. Mikulicz did, however, believe that the disease always involved and actually had its origin in the lacrymal glands, involving the salivary glands only at a later stage.

Within a few years, despite Mikulicz's published description and concept of the disease, which in retrospect are clear and definite in many respects, much confusion was precipitated by the appearance in the literature of many cases of bilateral chronic enlargement of the lacrymal and salivary glands, classified as Mikulicz's disease. It soon became apparent that the cause of enlarged lacrymal and salivary glands was not always as obscure as in the case reported by Mikulicz and that the course in some cases was that of a benign, self-limited condition; and in others, a rapidly fatal one. Pathologically, the tissues obtained for biopsy or at necropsy differed widely in various cases.

In 1907, Napp[2] declared the condition to be merely a symptom complex that might be produced by any one of several causes, such as leukemia, malignant lymphoma, atypical lymphomatosis, and tuberculosis. Two years later Howard[3] reviewed 81 cases collected from the literature and grouped them under three headings: (1) Mikulicz's disease proper, (2) malignant lymphoma, and (3) leukemia. This classification was found inadequate by Thursfield[4] who in 1914 made the first attempt to classify the syndrome on an etiologic basis. He divided all cases showing enlargement of the salivary and lacrymal glands into eight groups: a congenital, familial, and hereditary condition; Mikulicz's disease proper; Mikulicz's disease with involvement of the lymphatic apparatus; leukemia; tuberculosis; syphilis; gout; and sialodochitis fibrinosa. In 1927, Schaffer and Jacobsen[5] modified Thursfield's grouping, combining its eight categories into two large groups, Mikulicz's disease proper of unknown etiology, and Mikulicz's syndrome caused by leukemia, lymphosarcoma, tuberculosis, etc.

Although considerable progress was realized when it became evident that bilateral enlargement of the lacrymal and salivary glands was but a syndrome produced by a variety of diseases, an adequate histopathologic study of so-called Mikulicz disease proper is not available.

As will be discussed in other portions of this paper, it is important for purposes of treatment and prognosis that Mikulicz's disease be recognized and separated from other diseases which produce the so-called syndrome and simulate it clinically. Compared to other diagnoses which must be considered, none has been more difficult than the

differential diagnosis of Mikulicz's disease and malignant lymphoma, in both of which the lymphoid tissue is the prominent element. It is not surprising that in the past this has occasioned misdiagnosis or at least some uncertainty as to whether the lesion should be considered benign or malignant.

Because we, too, had experienced this uncertainty in respect to several such cases, we carried out a follow-up study of the patients on whom the diagnosis of malignant lymphoma of the salivary or lacrymal glands had been made, or considered. When this was done, it became apparent that in several of the cases the diagnosis had been correct, the patients having followed the usual course of malignant lymphoma with early death. Six patients, however, were found to be living and free of recurrences 9 to 16 years after surgical removal of the tumor. A study of the histologic sections of these 6 cases disclosed, in addition to diffuse lymphoid infiltration of the gland substance, a characteristic alteration in the duct epithelium, present in all. The thought was entertained that here might be a means of differentiating histologically these cases which in the past had been so confusing.

A further search in our own files and in those of neighboring laboratories provided us with a total of 18 cases which serve as the basis of the present study. In the various laboratories* from which these cases have been collected there had been a wide range of diagnoses. They included: chronic inflammation, Mikulicz's disease, metastatic carcinoma, atypical adenocystoma lymphomatosum, mixed tumor, lymphocytic leukemia, and malignant lymphoma. The last diagnosis was the one most commonly employed. For this reason, a number of these patients were considered to be suffering from malignant disease and treated accordingly.

Clinical Data (Table I)

Most of the patients had a history of a non-tender, progressively enlarging mass in the region of one or more salivary or lacrymal glands. Usually this was associated with no other symptoms, although 4 of the 18 having salivary gland involvement did complain of dryness of the mouth. Three patients who developed secondary infection in the gland experienced a moderate degree of temporary local tenderness. Four patients gave a history of increase and decrease in the size of the mass from time to time and two noticed rather rapid enlargement during the several months just prior to hospitalization.

Fifteen of the 18 patients were female.

* Massachusetts General Hospital, the Massachusetts Eye and Ear Infirmary, Boston City Hospital, New England Deaconess Hospital, Peter Bent Brigham Hospital, and the Harvard Tumor Diagnostic Service.

The ages ranged from 15 to 70 years. Twelve of the 15 women were between 37 and 59 years of age when the disease was first noticed. The ages of the men were 15, 39, and 70 years.

TABLE I

Clinical Data for Eighteen Cases of "Mikulicz's Disease"

Case no.	Age	Sex	Known duration (years)	Gland and location	Number of glands involved	Treatment	Follow up (years)
1	35	F	1	Both parotid glands and both submaxillary glands	4	Surgical excision and x-ray therapy	6
2	61	F	12	Both parotid glands and both submaxillary glands	4	Surgical excision and x-ray therapy	5¾
3	62	F	1/3	Both parotid glands and both submaxillary glands	4	Surgical excision	2
4	39	F	5	Both lacrymal glands	2	Surgical excision	3⅔
5	47	F	1	Both parotid glands	2	None	Necropsy
6	55	F	11	Both parotid glands	2	None	Necropsy
7	70	M	1	Left parotid gland and left submaxillary gland	2	Surgical excision	7
8	59	F	1	Left parotid gland and left submaxillary gland	2	Surgical excision	Necropsy
9	37	F	5/12	Right parotid gland	1	Surgical excision	2/3
10	39	M	1	Right parotid gland	1	Surgical excision	14
11	48	F	1	Right parotid gland	1	Surgical excision, x-ray therapy, and radium seeds	16
12	47	F	1⅔	Left parotid gland	1	Surgical excision	1
13	50	F	10	Left parotid gland	1	Surgical excision	1
14	56	F	2/3	Left parotid gland	1	Surgical excision	13½
15	37	F	5/6	Left parotid gland	1	Surgical excision and x-ray therapy	9½
16	40	F	1/6	Left parotid gland	1	Surgical excision	12
17	69	F	2	Left parotid gland	1	Surgical excision and radium seeds	10
18	15	M	1	Left submaxillary gland	1	Surgical excision	5⅓

The duration of the masses before the patient came to the hospital ranged from 2 months to 12 years. In most cases it was 1 to 2 years. Of 3 long-standing cases, one had enlargement of a single parotid gland for 10 years; another, enlargement of both parotid glands for 11 years; and still another, of both parotid and submaxillary glands for 12 years.

The gland, the number, and the combinations of glands showed remarkable variation in this series. In 9 cases there was involvement of a single parotid gland; in one case, a single submaxillary; in 2 cases, a single parotid and a single submaxillary. There were 3 cases with involvement of both parotid and submaxillary glands, and 2 cases of both parotid glands. In one case the disease was confined to the lacrymal glands. No case was encountered in which all six glands were involved.

A follow-up study ranging from 1 to 16 years was possible on 14 patients who underwent surgery (Table I). In none of these was there clinically any recurrence of the disease locally or spread to other organs. Necropsies of 3 patients, who died of apparently unrelated diseases, failed to show any evidence of malignant lymphoma or of disease in any other organ similar to that present in the salivary glands.

If, for the purpose of follow-up studies, we exclude the 3 patients who died, 15 remain who had surgical excision of one or more of the glandular masses. Of 8 of these patients, on whom specific information was available, one had implantation of radium seeds; another, radium seeds and x-ray therapy; 3 had x-ray therapy; and 3 others were followed in the Out-Patient Clinic with a diagnosis of probable malignancy.

Pathologic Findings

GROSS EXAMINATION

In most cases, the only abnormal finding at operation was diffuse, symmetric enlargement of the salivary gland (Fig. 1). In others, however, the disease process was focal, giving the involved portions the appearance of nodularity in contrast to adjacent normal gland tissue. When diffusely enlarged, the glands might measure up to 7 by 5 by 4 cm. Except in secondarily infected cases, there was no capsular thickening and the surgical removal was not difficult. The adjacent lymph nodes were not enlarged. The gland retained the normal lobular pattern and general configuration of a salivary gland.

On section, the specimen cut with somewhat rubbery resistance, presenting a surface which was smooth, glistening, and homogeneously pinkish tan. The most striking aspect of the cut surface was the preservation of the lobular architecture and the marked enlargement of the individual lobules, the latter often measuring up to 1 to 2 cm. in greatest diameter. The lobules were separated by thin fibrous septa.

Three specimens in this series contained cystic structures measuring up to 1.5 cm. in diameter, and in one case, thin, tan-brown fluid was described as contents of the cysts.

MICROSCOPIC EXAMINATION

The histologic picture of all 18 cases was so similar as to leave no room for doubt that a single disease process was common to all. This consisted of two co-existing fundamental changes: (1) a gradual lymphoid infiltration and proliferation within the lobule, with subsequent atrophy and loss of acinar tissue until there was complete replacement of the glandular parenchyma by the lymphoid tissue; and (2) an alteration of the ducts, characterized by a typical intraductal cellular proliferation, gradual narrowing of the ductal lumen leading to the formation of a compact cellular island lying in a stroma of lymphoid tissue, and, finally, the deposition of a hyalin-like substance which in time might completely replace the altered duct structures.

Parenchymal Changes

The earliest evidence of involvement of a lobule, in so far as the lymphoid tissue was concerned, was the presence of a scattering of lymphoid cells—usually mature lymphocytes—about one of the intralobular ducts (Figs. 2 and 3). In time, the accumulation of lymphoid tissue became greater, adjacent ducts were surrounded, and groups of immature lymphoid cells might be identified, indicating proliferation. The lymphoid involvement followed a characteristic pattern, first occurring more or less centrally in the lobule and then extending toward the periphery of the lobule until complete replacement of acinar tissue had taken place. When this occurred, the lymphoid tissue, except in rare instances, appeared to remain contained within the lobular septa and did not spread across into adjacent lobules (Fig. 2).

The arrangement of the lymphoid tissue (Figs. 5 and 6) was interesting in that it did not have the appearance of normal lymphatic tissue. Well circumscribed lymph follicles usually were not present. Rather, the numerous aggregations of immature lymphoid cells ordinarily seen in the follicle occurred in nondescript clumps, in streams, or in swirling masses. These were most frequently seen lying adjacent to fibrous trabeculae or about ducts and blood vessels. This lack of discrete follicular organization gave more of an appearance of infiltration, and undoubtedly has been one of the deciding factors responsible for the diagnosis of malignant lymphoma previously made in some of these cases. The picture was further complicated by the presence of moderate to large numbers of similar immature cells scattered throughout the stroma, occurring singly or in clumps of two or three. Many of these cells were in active mitosis. Plasma cells, eosinophils, or polymorphonuclear neutrophils were rare except in cases complicated by secondary infection.

Silver stains (Fig. 16) on sections from cases of about 1 year's duration in which there was complete replacement of the lobule by lymphoid tissue showed a fine background of reticulum similar to that of lymph nodes, but absence of the usual prominent follicular pattern. In cases of longer duration, hyalinization of the stroma similar to that seen in lymph nodes which have been the site of chronic inflammation was very prominent (Fig. 7). The lymphoid cellular infiltration, although less in amount, remained of the same character as that seen in cases of shorter duration.

The changes in the acini were coincident with the advent of the lymphoid infiltration and appeared to be those of simple pressure atrophy (Fig. 8). They first occurred more or less centrally, with gradual and progressive involvement of the lobule as it was replaced by lymphoid tissue. The acini immediately adjacent to the lymphoid tissue became compressed and separated, the nuclei hyperchromatic, and the cytoplasm more darkly acidophilic. As the lymphoid tissue increased in amount the acini became smaller and finally fragmentation and disintegration occurred. There was, in addition, loss of the normally present fat. There were no focal lesions in the acini, and the infiltration by lymphoid cells was wholly periductal. The lymphoid proliferation continued until the entire glandular parenchyma, with the exception of the ducts, was replaced.

Changes in Ducts

Normally, the ducts (Fig. 9) were lined by regular cuboidal or columnar cells with a centrally or basally placed single or double row of rounded nuclei. It has been our experience that when any alteration was noted in a given duct, several of the early changes might be observed. Although the organization of the lining epithelial cells remained intact, the nuclei became hyperchromatic, less regular in outline, and ovoid or spindle-shaped (Fig. 10). The cytoplasm changed from the normally bright acidophilic pink to a more basophilic purple. Later in the early stage, there was an increase and piling up of nuclei with beginning loss of polarity in the position of epithelial cells but also external to these, yet within the basement membrane, in a location which normally would be accorded to myoepithelial cells (Figs. 4 and 11). More advanced stages of alteration were characterized by the presence of a greater number of nuclei of both cell types, apparently indicating that a continued proliferation had occurred. As might be expected, this resulted in a thickening of the layer of cells between the basement membrane and the lumen, and there was subsequent narrowing of the lumen. This cellular proliferation was accompanied by a

prominent disorganization and loss of polarity, so that in a more advanced phase of the early stage the cells appeared to lie in all directions, the "epithelial" layer persisting as a confused mixture of epithelial and myoepithelial cells (Figs. 3 and 4). This disorganization was further complicated and increased by the migration of lymphoid cells into the altered ducts. When this occurred, even greater changes in the cells were observed. There was an obvious loss of cellular cohesion. Many showed hydropic degenerative changes in which pyknotic nuclei of round, ovoid, reniform or spindle shape appeared to lie suspended in vacuolated spaces containing a few scattered acidophilic granules suggestive of remnant cytoplasm. There was considerable variation from one duct to another and although one duct might show the degenerative changes described, another nearby might show none. An additional finding of interest, although not manifest in every duct, was the presence of normal appearing mitotic figures, in some ducts numbering up to twenty.

The proliferation of cells continued, gradually narrowing the lumen until it was completely obliterated. At this time the involved ducts assumed the form of solid, branching, densely cellular cords lying in a stroma or sea of lymphoid tissue (Figs. 12, 13, 14, and 15). Because of this rather striking appearance and for convenience in differentiating these from unaltered ducts, we have elected to call them "epi-myoepithelial islands."

The outline of the epi-myoepithelial islands followed in general that of the ducts from which they obviously arose. In cross section they were roughly circular or ovoid, and on longitudinal section they appeared as straight or branching cords. They were, however, usually one to two times greater in diameter than normal ducts, and occasionally they might reach five to six times the diameter of an intralobular duct and form relatively large, discrete sheets of cells. They were enclosed by an intact basement membrane which was usually visible with the ordinary stains, but particularly well shown with silver stains (Fig. 16).

If one excluded the migrating lymphoid cells which usually were present in varying numbers, the islands were composed of two types of cells, epithelial and myoepithelial. Their separation into two distinct cell types, however, was not easy. Because of the disorganization and indefinite cell borders the distinction was made almost wholly on the character of the nuclei. We recognized as epithelial those cells in which the nuclei were fairly large and ovoid, circular, or irregularly reniform. These nuclei were generally vesicular with a fine scattering of clumped or granular chromatin. In contrast, the myoepithelial cells

were thin and elongated with prominent, usually hyperchromatic, spindle-shaped nuclei, on cross section triangular, with rather poorly defined, fibrillar, acidophilic cytoplasm (Fig. 12). Usually it was only when they were present at the periphery of the island that the myoepithelial cells could be distinguished from the lymphoid cells and identified with any degree of certainty. Attempts to distinguish these cells by means of special stains, including the Masson erythrosin-saffron stain employed and recommended by Kuzma[6] in his study of breast tumors, were unsuccessful.

Following the intraductal cellular proliferation, the obliteration of the duct lumen, and the formation of an epi-myoepithelial island, a second characteristic change, the deposition of hyalin (Figs. 13 and 14) occurred.

Here, the hyalin, as seen elsewhere in the body, was homogeneous and brightly acidophilic. It was of interest that in the early stages of development, it appeared to occur in two rather distinct positions in regard to its relationship with the cells composing the island. When in the form of droplets or globules, one or more of the hyperchromatic nuclei lay against the edge of the material (Figs. 13 and 14) and a thin membrane, which appeared also to include the nucleus, extended around the droplet's edge. This was especially well demonstrated by use of silver stains and strongly suggested that the material was intracellular, the nucleus being pushed to one side. Elsewhere, however, the hyaline material seemed to thread its way between the cells and appeared to be extracellular. Thus, in a given island, the exact positional relationship of the cells with the hyaline material was just as indefinite as that existing between one cell and another.

A very definite correlation existed between the degree of duct alteration and the duration of the disease clinically. This was of such degree as to permit one to estimate with considerable accuracy from a given slide what the approximate duration of the disease might be. Those cases in which the disease had been clinically active for about 1 year showed minimal deposition of hyaline material, those active up to 5 years, moderate deposition; while cases with active symptoms for 10 years or more, exhibited severe hyaline changes in which there was often essentially complete replacement of the islands so that they persisted throughout the stroma as scattered, densely acidophilic, almost acellular bodies (Fig. 7).

Examination of many of the epi-myoepithelial islands disclosed that there was no uniformity from one island to the next in the proportion of myoepithelial to epithelial cells, one showing epithelial cells in predominance, another myoepithelial, and still another, a more even mix-

ture. There was evidence to suggest that those islands which contained a greater number of myoepithelial cells were associated with a greater deposition of hyalin, while those in which there was a predominance of epithelial cells showed attempts at formation of duct-like structures which contained acidophilic granular material which differed from hyalin and had the staining reactions of duct secretions.

Some intralobular and interlobular ducts showed a change in the epithelium which was similar to that previously described for the smaller ducts, except that the process did not go on to obliteration of the lumina. In contrast, these were frequently dilated (Fig. 2) and it seemed most probable that it was by cystic dilatation of larger ducts that cysts of macroscopic size were produced in several cases. The epithelium showed proliferative activity, varying from three to ten cells in height. It might in areas be thrown into small projections, although these in no way resembled the true papillary formations such as are seen in papillary adenocystoma lymphomatosum. In the larger cysts, the lining cells were supported by an irregular layer of dense, homogeneous, usually acellular, hyaline connective tissue. Occasionally a cystic structure was seen to be connected with an epi-myoepithelial island. The dilated ducts or cysts might contain masses of lymphocytes, acidophilic amorphous matter or needle-like crystals, or small, rounded, bluish, calcified bodies. In no instance were cholesterol crystals identified.

The Lacrymal Gland

Although little has been said specifically about the lacrymal glands, the gross and microscopic findings in the one case in this series were very similar to those just described for the salivary glands.

Selective Review of the Literature

An attempt to find in the literature other cases with similar microscopic findings met with only slight success. Scattered reports during the past 30 years have called attention to diffuse lymphoid infiltration of the salivary glands associated with duct epithelial changes. In most of these articles, however, the latter aspect of the lesion was considered of minor importance, emphasis being placed on the lymphoid hyperplasia. Follow-up studies in most cases suggested disease of chronic type, but opinions differed as to whether or not the lesion was benign or malignant. No large series of cases in which definite conclusions were reached was found.

Smith and Bump,[7] in 1928, reported a case of a 62-year-old woman who was admitted because of bilateral parotid swellings of approxi-

mately 1 year's duration. At operation, a reddish encapsulated mass was removed from the region of the left parotid gland. The initial histologic report was "lymph node containing metastatic carcinoma which in places had a duct-like appearance." A subsequent diagnostic consideration by this same observer was "embryonal carcinoma, possibly from the remains of a branchial cleft." The final diagnosis rendered after consultation with another pathologist was Mikulicz's disease. Although these authors drew attention to the ductal epithelial changes and stated that by serial sections they had shown these changes to extend along the duct system, they believed the duct alteration to be squamous metaplasia and destruction due to infiltration by lymphocytes.

Sidahara,[8] in 1937, reported a case in a middle-aged man of lymphosarcoma of the parotid gland cured by surgical removal. His photomicrographs show very clearly the duct changes and epi-myoepithelial islands so characteristic of the lesion being described.

In 1938, Swinton and Warren,[9] reviewing their series of parotid gland tumors, found 7 cases which they considered of particular interest from the standpoint of differential diagnosis. All of these cases occurred in women, with an average age of 55.9 years. The histologic picture described is consistent with that presented in this paper; however, these authors also considered the duct change to be squamous metaplasia. Follow-ups of 1 to 6 years on these cases showed no evidence of recurrence in any case and the authors believed the lesion to be a benign, chronic inflammatory process.

Lehman and Leaman,[10] in 1940, reported a case of a 55-year-old woman who complained of sore eyes for 3 years and dryness of the mouth for 2 years. Physical examination disclosed swellings over the regions of both lacrymal glands and one salivary gland. These authors considered the lesion to be Mikulicz's disease proper. Although they did not emphasize it, the typical alteration in the duct epithelium was evident in the photomicrographs.

In 1942, Skorpil[11] presented in a paper on benign lymphoma of the salivary glands an account of 2 cases of unilateral parotid swelling occurring in a 15-year-old boy and a 34-year-old woman which had been followed for 3 and 16 months, respectively. He described the duct changes in detail and, although he found no definite cause, he believed the pathologic changes to be most probably of infectious origin.

Of these 11 cases, all but 2 were of females, and all but the 15-year-old boy reported by Skorpil[11] fell into the age group of the fourth to seventh decade.

Differential Diagnosis

1. Chronic Inflammation (Figs. 17 and 18). The illustrations show the usual form of chronic inflammation seen in the salivary glands, frequently associated with calculi. Grossly there is fibrosis, atrophy, and distortion of lobular architecture. Microscopically, the fibrosis, loss of acinar tissue, and infiltration by chronic inflammatory cells composed of plasma cells, lymphocytes, and eosinophils serve to differentiate the two diseases. In addition, the ducts which persist usually show changes quite different from those seen in Mikulicz's disease (Fig. 18). They may occasionally show squamous metaplasia which, again, is readily distinguished from the characteristic ductal epithelial change previously described. Sixty cases of chronic inflammation of the salivary glands were studied as control material; in none were epi-myoepithelial islands found.

2. Adenocystoma Lymphomatosum (Fig. 19). Adenocystoma lymphomatosum should not offer much difficulty in differential diagnosis. Grossly, it has a characteristic appearance, and, in contrast to the features previously ascribed to Mikulicz's disease, occurs as a discrete, encapsulated, roughly rounded, soft or cystic mass lying within or protruding from the substance of the gland. Microscopically, the typical tall, eosinophilic, columnar epithelium with a double row of nuclei, the usual papillary character, and the lymphoid stroma with well formed follicles, readily serve to differentiate the two. Fifteen cases of adenolymphoma from our own files were studied as control material.

3. Metastatic Carcinoma. Metastatic carcinoma is included as a possibility only for emphasis because this diagnosis was rendered on one case in this series and in one found in the literature. Although it should be possible to differentiate the two in permanent sections, one could readily imagine that a pathologist unfamiliar with the lesion, when presented with a few fragments for frozen section in which the epi-myoepithelial islands were prominent might easily give this diagnosis serious consideration (Fig. 15).

4. Malignant Lymphoma. Of the several diseases from which Mikulicz's disease must be differentiated microscopically, the most important one is malignant lymphoma (Figs. 20 and 21), for it is to this condition that it bears the greatest resemblance. Ten cases of malignant lymphoma of the salivary gland proved by necropsy or subsequent lymph node biopsy were studied.

In contrast to Mikulicz's disease in which preservation of lobular architecture is a characteristic feature grossly, in the cases of malig-

nant lymphoma the prominent finding is that of a fairly discrete, nodular tumor in a portion of the gland in which the lobular architecture is absent. Three differences found histologically were as follows: (1) Whereas in the benign disease, the lymphoid tissue is with rare exceptions contained within the lobule and the interlobular septa are preserved, in malignant lymphoma the cells soon pass in all directions from one lobule to the next and septa are obliterated. (2) The cell type, as in the stem cell and Hodgkin's lymphomas,[12] will undoubtedly provide a measure of security in the diagnosis, and it is probable that only in the lymphocytic type of malignant lymphoma will there be a real danger of misdiagnosis. Although 17 of the 18 cases in this series showed a predominantly mature lymphocyte type composing the stroma, there was one case in which immature cells of the lymphoid series occurred in considerable numbers. In addition, many cells with double nuclei were present which could be justifiably considered atypical. Sections from this case were shown to several competent pathologists and each made a diagnosis of malignant lymphoma. However, typical epi-myoepithelial islands were present, and in view of what would otherwise represent a clinical cure of malignant lymphoma, we have little hesitation in including the case in the benign group. In several other cases the number of lymphoid cells in active mitosis was great. Although this point must await confirmation by the study of additional cases, it seems worth while at this time to suggest that in some cases the degree of lymphoid hyperplasia may be great and the character of the cells disturbing. (3) The typical epithelial changes of the ducts with the formation of the epi-myoepithelial islands, in our experience, has been the most dependable way of distinguishing the two diseases. In none of the cases of malignant lymphoma were these changes found. In lobules involved by malignant lymphoma the acinar tissue is often replaced, but aside from perhaps slight atrophy the ducts usually remain, with essentially unaltered epithelium.

Although it would appear, from this study, that the presence of the characteristic ductal epithelial change with the formation of the epi-myoepithelial islands is unique and probably pathognomonic of Mikulicz's disease, it seems prudent to suggest that until additional cases of this disease are studied, a conservative approach to the diagnosis, utilizing all three of the differential points, be employed.

Discussion

In considering the possibilities of pathogenesis in this disease it was necessary to determine, if possible, which of the two prominent findings histologically—the ductal epithelial change or the lymphoid tis-

sue—was the fundamental defect. This was difficult for several reasons. First, changes in the ducts are not observed in the absence of at least minimal lymphoid infiltration, and second, the lymphoid element is by far the more impressive.

Although we have only morphologic evidence, it is our opinion that the primary lesion in this disease is an involvement of the duct system, manifested by the duct changes previously described, and that the lymphoid tissue is simply a secondary response evoked by that basic defect. The following observations support this contention: (1) In no other disease of the salivary or lacrymal glands has the typical ductal epithelial change been found; whereas, the lymphocyte is commonly seen in chronic inflammation. Well developed follicles in close relation to ducts and heavy infiltration of the duct epithelium by inflammatory cells are frequent in the usual case of chronic inflammation. It seems reasonable to expect that this must produce considerable trauma to the duct epithelium and is possibly an agent in the development of squamous metaplasia. The fact that this occurs in chronic inflammation and does not result in a change in the duct epithelium similar to that found in Mikulicz's disease is strongly suggestive that it is not the migration of lymphoid cells into the epithelium over a relatively long period of time which effects the characteristic changes noted. (2) The character of the lymphoid tissue, which appears to respond to certain growth controls to the extent that lobular architecture is preserved, is more in keeping with a response of a secondary nature in contrast to an uncontrolled invasive one, such as that seen in malignant lymphoma. (3) The spotty, but frequently observed involvement, in which a normal lobule may be immediately adjacent to a lobule which is partially or completely replaced by lymphoid tissue (Fig. 2), and the varying amounts of lymphoid tissue, usually in proportion to the ductal epithelial change and confined to the periductal area, are, again, more than suggestive that the disease occurs primarily in the ductal system, involving some radicals and sparing others. Relative to this point, it is of particular significance that Johnson and Goodpasture,[13] in their cases of mumps parotitis produced experimentally by injection of infectious material into Stensen's duct in monkeys, were similarly impressed by the irregular, focal involvement of lobules.

Arguments in favor of the lymphoid tissue being the primary defect are (1) the observation that the infiltrate is composed almost solely of cells of the lymphocytic series, a finding with which we cannot make an analogy in any other benign disease process except Hashimoto's struma of the thyroid gland, (2) the character of the lymphoid tissue with its

lack of organization into a discrete follicular pattern as is usually the case in other conditions in which lymphoid tissue represents an inflammatory reaction, and (3) the observation that in many of the ducts in the early stages, before the epi-myoepithelial island is formed, the epithelium shows marked distortion and disorganization, and the lumen is filled with masses of lymphocytes, indicating the migration of the lymphocytes through the duct wall into the lumen.

An attempt to determine the etiology of this disease was unsuccessful. Most patients were clinically well aside from the asymptomatic enlargement of their salivary or lacrymal glands. There was no evidence of a familial tendency nor for explanation on the basis of exposure to toxic materials. Syphilis, which had been considered in some of the earlier case reports, seemed justifiably ruled out on the basis of negative serologic tests on 12 of the patients in this series. Avitaminosis, which again was considered by some authors, could not be confirmed by a study of the social histories of our own cases. These cases differed clinically from the usual ones in which chronic inflammation and calculus are found. In no case did a severe episode of pain on swallowing bring the patient to the hospital, and in none were calculi of more than microscopic size found. In none of the patients were the initiating symptoms those of acute inflammation, although as stated earlier, several cases did become secondarily infected and were then characterized by episodes of redness, pain, and swelling. Histologically, there was no evidence of granuloma formation. The lack of a strong allergic history clinically and the absence of eosinophils histologically tended to rule against this lesion being of the more usual type of allergic origin. In neither histologic sections nor in smears of fluid expressed from ducts in several cases was there evidence of a parasitic etiology. A careful search of numerous sections from all cases for an alteration suggestive of viral etiology, such as the giant cells in the duct epithelium described by Farber and Wolbach,[14] was unsuccessful, and no relationship to mumps parotitis could be detected.

Since the etiologic mechanism in this disease was not established during the course of study, we are left to consider the clinical and morphologic findings which did result with the hope that these may provide information and some better understanding of the nature of the disease.

That the disease is benign and chronic in character appears clearly evident from the long clinical observation of most of the cases in this series and the detailed examination of the 2 cases which were necropsied. That it differs, however, from the usual forms of chronic inflammation is made apparent by the distinctive clinical history and the

gross and microscopic appearances. These observations, plus the rarity of the disease and the frequent bilateral glandular involvement, would tend to lead one away from the possibility of duct obstruction, the most common offending mechanism in chronic inflammation, as being the etiologic agent also in Mikulicz's disease.

The fact that 15 of the 18 cases (83.3 per cent) and 9 of the 11 (81.8 per cent) found in the literature occurred in women is of more than passing interest. This sex incidence is indeed at variance with that of the usual form of chronic inflammation, which is more frequent in males. It is difficult to know what significance, if any, should be attached to the fact that a majority of the female patients developed the disease at about middle age. An analysis of the time relationship of the menopause and the onset of the disease in the women of this series demonstrated no significant correlation, since the onset occurred both before and after the menopause.

This tendency for the disease to occur in middle-aged females would provide an interesting problem for the endocrinologist were it not for the presence in the current series of 3 cases, about which there could be no doubt, occurring in males aged 15, 39, and 70 years. The physical examinations of these individuals, 2 of whom were seen in the hospital at relatively frequent intervals, failed to reveal evidence of any endocrine abnormality.

Taken separately, the age and sex incidence shown by this disease appears to offer little in way of explanation. When considered together, however, and in combination with the microscopic finding of diffuse lymphoid infiltration, the intriguing possibility of some relationship to Hashimoto's struma of the thyroid is presented. However, examination of the clinical histories of the cases in our series as well as those found in the literature failed to support this possibility, since in no case was there a history of thyroid disease either before or at the time of admission for salivary glandular swelling. Further, Statland, Wasserman, and Vickery,[15] examining 51 patients with Hashimoto's struma from this hospital, found only one who had swelling of the salivary glands.

In considering other diseases which manifest enlargement of the salivary glands, a series of papers by Sjögren[16-25] describing a condition consisting of keratoconjunctivitis sicca, bucco-pharyngo-laryngitis sicca, swelling of the salivary glands, and polyarthritis, usually of the rheumatoid type, were encountered. The possibility of a relationship between Mikulicz's disease and this syndrome appeared more likely

when it was learned that Sjögren's syndrome also occurred almost exclusively in women past the age of 40 years. It was strengthened still further by Sjögren's description of the histopathology of the parotid gland in which lymphoid infiltration and duct changes are the prominent findings. One of Sjögren's photomicrographs[22] (p. 76) depicts an epi-myoepithelial island lying in a stroma of lymphoid tissue. In view of the similarity of some of the clinical and pathologic aspects of these two diseases, our material is being re-investigated. The results of that study will be reported separately.

Summary and Conclusions

The clinical and pathologic aspects of Mikulicz's disease have been studied in a group of 18 cases.

The disease is benign and chronic and may involve one or more salivary or lacrymal glands. At variance with Mikulicz's original belief that the disease is always bilateral and always involves the lacrymal glands, it has been found that the disease is frequently confined to only one salivary gland and affects the lacrymal glands less often than it does the salivary glands.

It occurs predominantly in women, in the fifth and sixth decades.

Grossly, the disease is characterized by preservation of the normal lobular architecture and diffuse enlargement, features which tend to distinguish it from other diseases of the salivary or lacrymal glands.

Histologically, the disease is characterized by replacement of the acinar parenchyma by lymphoid tissue and an intraductal proliferation of two cell elements, epithelial and myoepithelial, with the formation of epi-myoepithelial islands. The presence of the latter offers the most dependable means by which Mikulicz's disease may be distinguished from malignant lymphoma with which it has most often been confused.

On the basis of certain clinical and pathologic similarities to Sjögren's syndrome, it seems likely that Mikulicz's disease is not a distinct clinical and pathologic disease entity as previously believed, but merely one manifestation of a more generalized symptom complex known as Sjögren's syndrome. This possibility is being studied and if confirmed, a further relationship to rheumatoid arthritis and associated diseases is strongly suggested.

We wish to express our appreciation to Drs. Frederic Parker, Jr., Shields Warren, William Meissner, Olive Gates, and Parker Heath for granting permission to use their cases in this study. Most of these individuals also reviewed the slides on these 18 cases and offered valuable suggestions. We wish also to acknowledge our debt to the late Dr. Tracy B. Mallory for his opinions, interpretations, and kindly advice in the early stages of this work.

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[*Illustrations follow*]

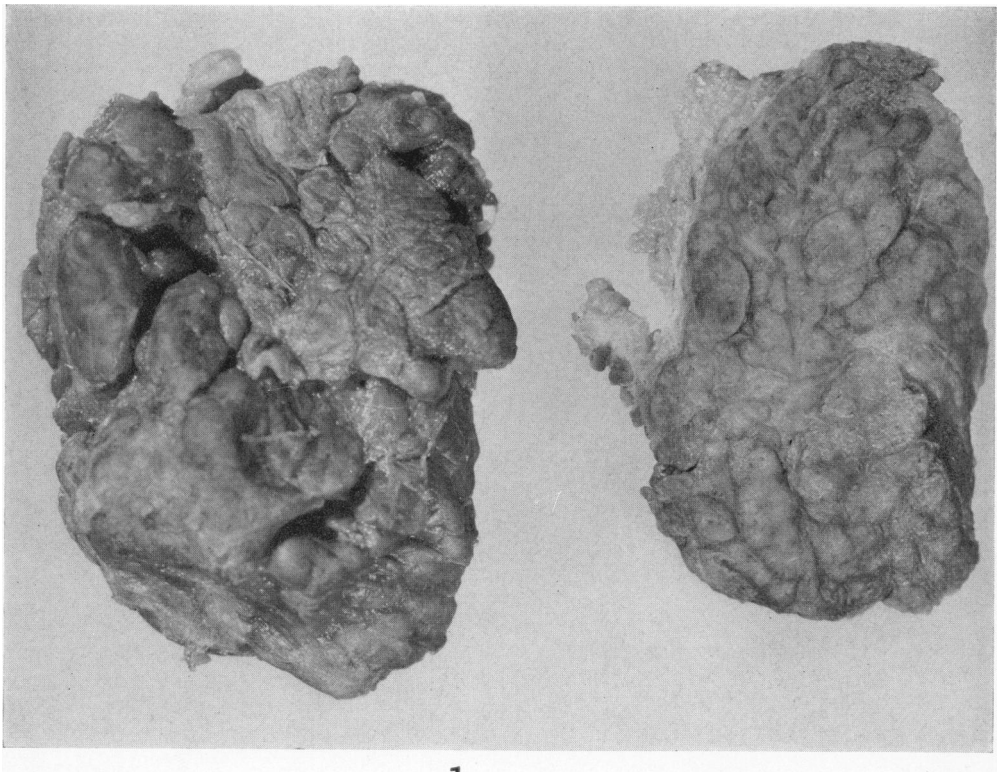
LEGENDS FOR FIGURES

Figures 1 to 4 and 6 to 16 inclusive are of "Mikulicz's" disease.

FIG. 1. Parotid gland (actual size) showing the typical gross appearance. The preservation of lobular architecture and enlargement of individual lobules may be noted.

FIG. 2. Section showing lobular preservation and the sharp confinement of lymphoid tissue to certain lobules. The darker appearing lobules or portions of lobules are those in which the acinar parenchyma has been replaced by lymphoid tissue. Dilated ducts and scattered epi-myoepithelial islands are present. × 9.

FIG. 3. Area showing early periductal lymphoid infiltration and adjacent normal glandular parenchyma. There is disorganization of the epithelium in the centrally placed ducts. For comparison with normal duct in upper right corner. × 100.



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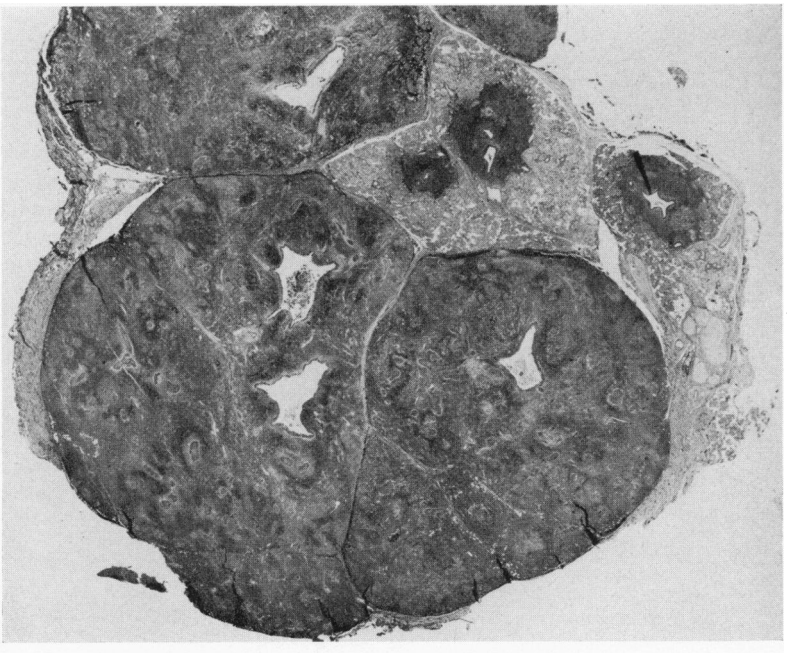

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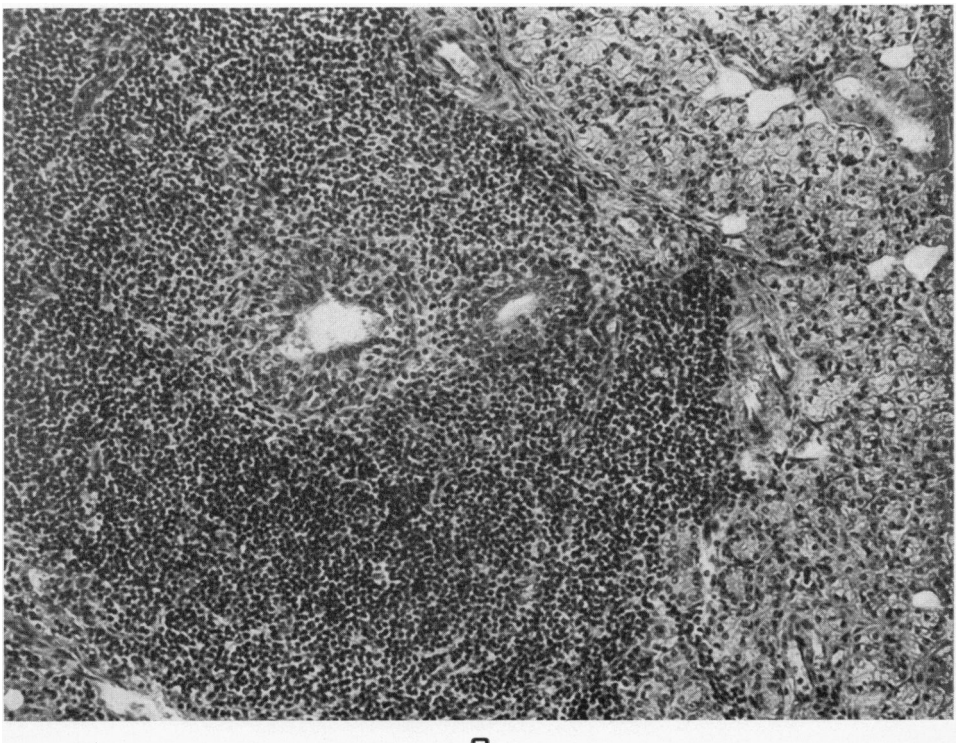

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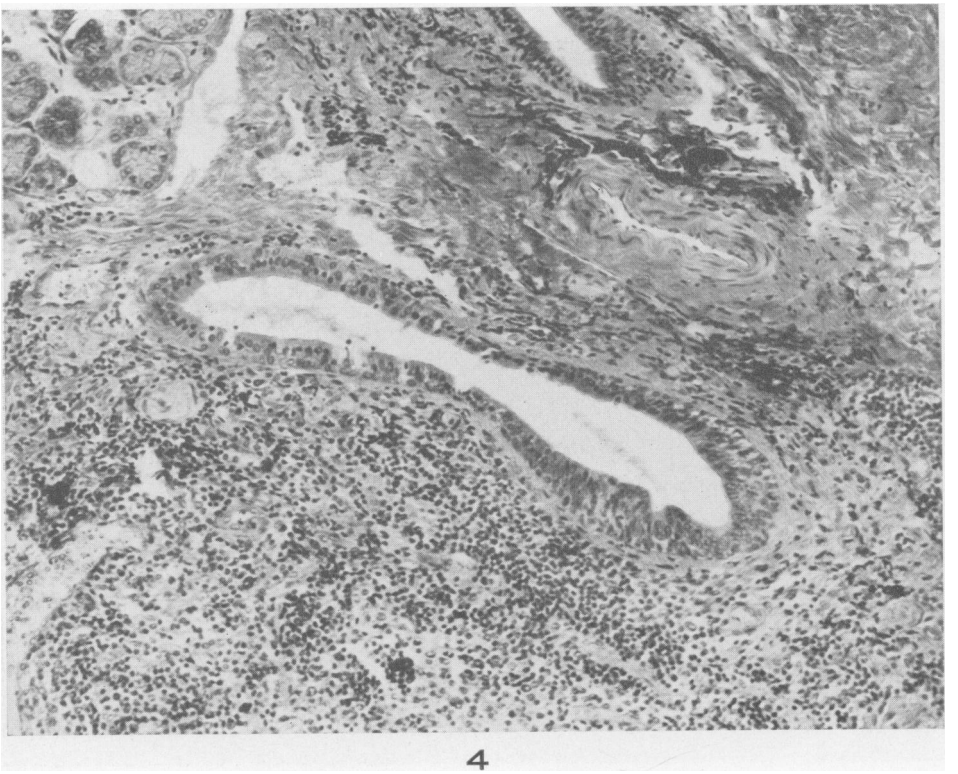
FIG. 4. A duct showing partial change. The left half has normal epithelium composed of cells of uniform size, shape, and polarity with relatively pale-staining cytoplasm. In the right half, the epithelium shows piling-up of cells, poor definition of cell membranes, variation in size and shape, distinct disproportion of nuclear size to the amount of cytoplasm, and loss of polarity. × 100.

FIG. 5. Section showing the character of the lymphoid stroma. × 180.

FIG. 6. Higher magnification of another area of the lymphoid stroma. × 400.



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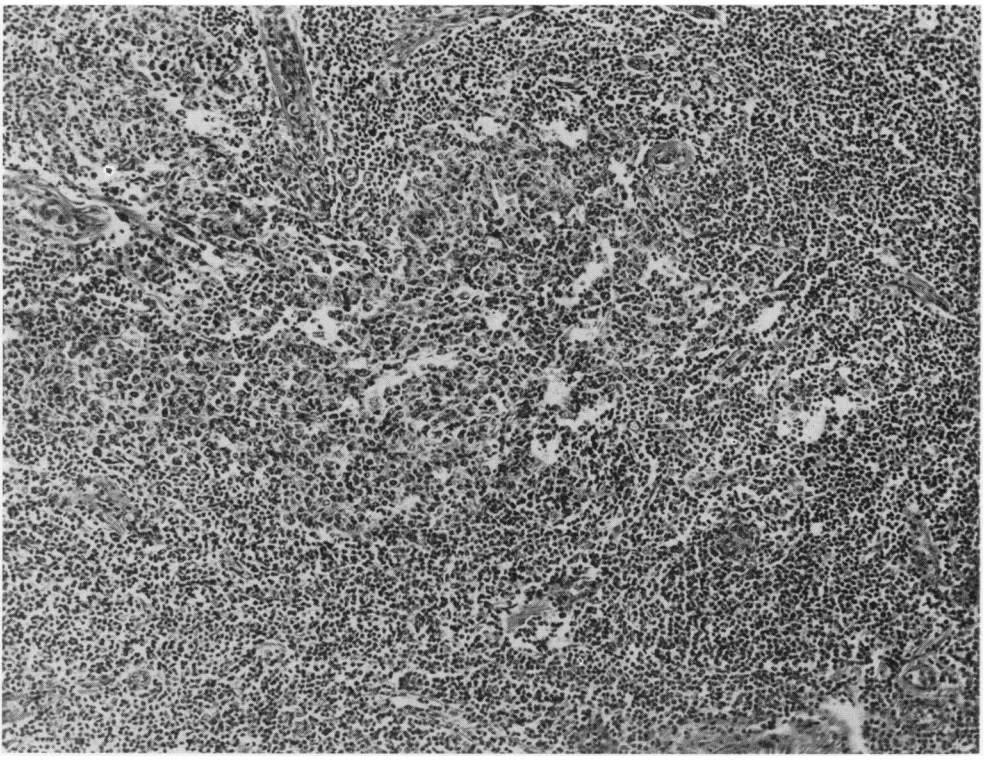

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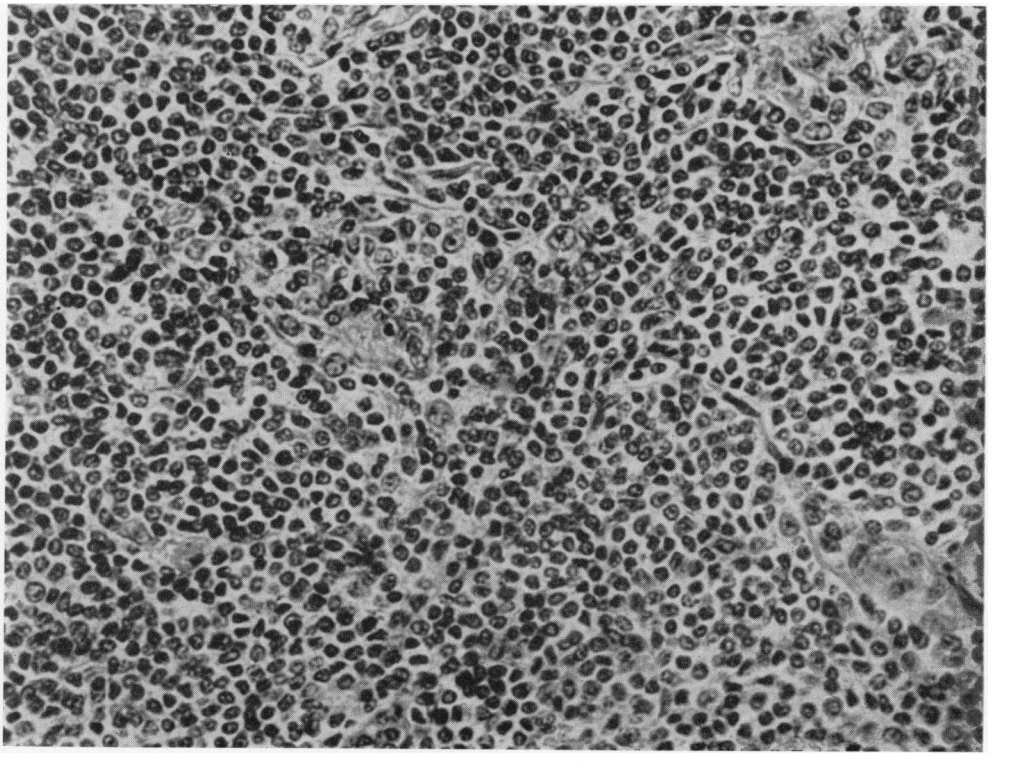

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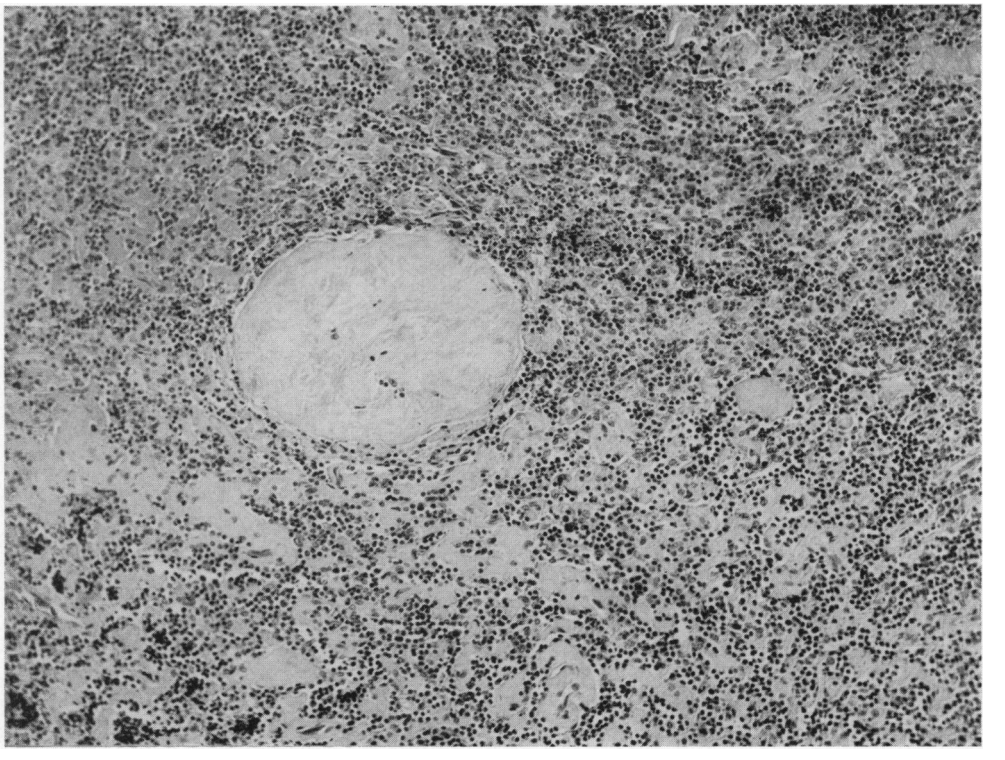
FIG. 7. From a case in which the disease had been active for 10 years. Of note are the hyalinization of the stroma and an epi-myoepithelial island. × 180.

FIG. 8. Area showing separation and atrophy of acini due to infiltration by lymphoid tissue. × 400.



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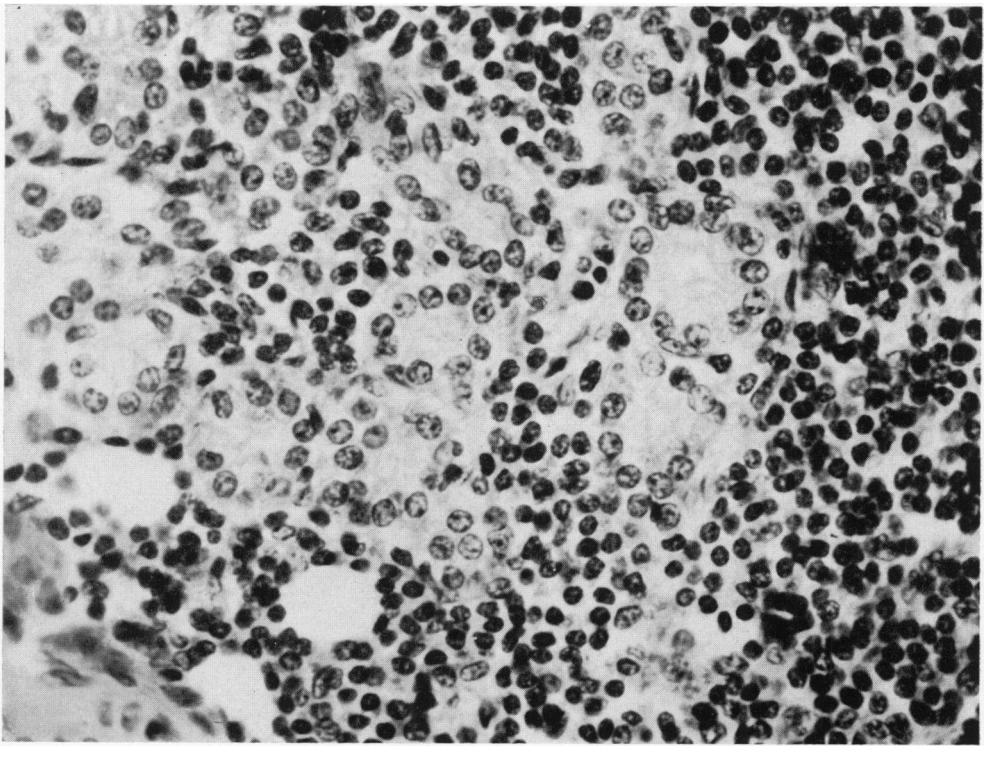

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FIG. 9. Section of normal salivary gland showing a normal duct, acinar tissue, and fat. × 400.

FIG. 10. Duct showing very early change. There is a slight increase in the number of cells of the epithelial layer, especially in the basal region. × 400.

FIG. 11. A duct showing advanced alteration characterized by an increase in the number of cells, loss of polarity, disproportion of nuclear size to cytoplasm, and narrowing of the lumen. × 400.

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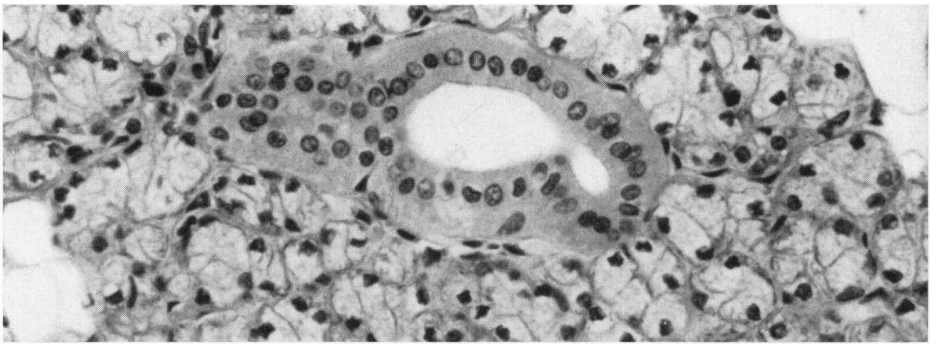

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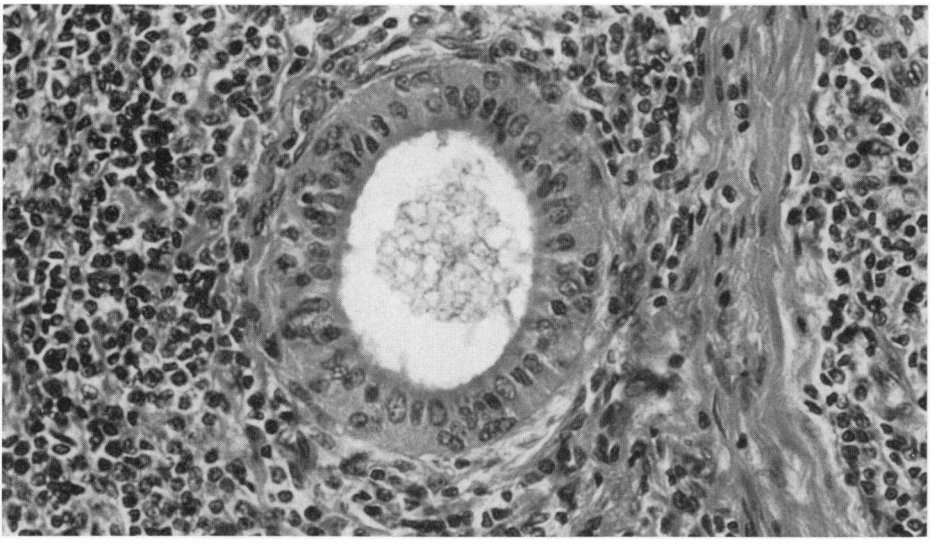

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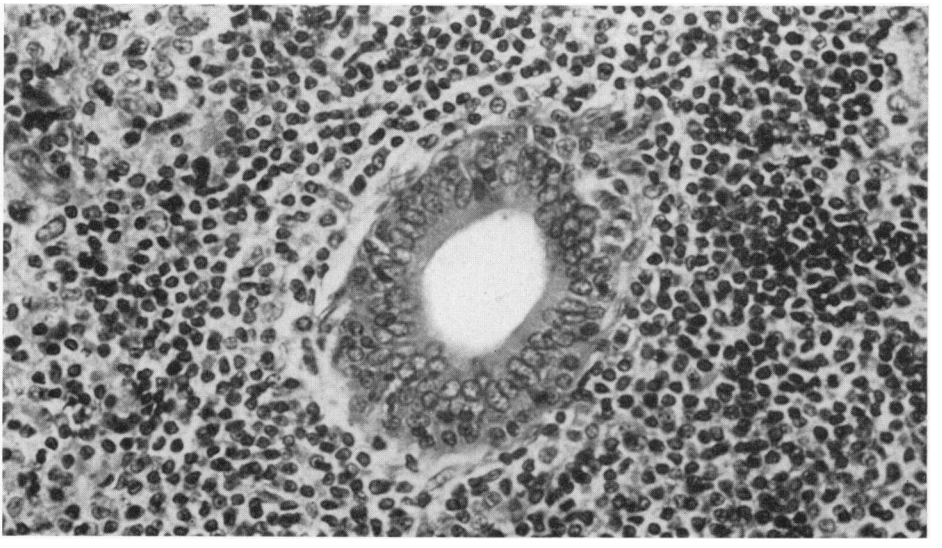

FIG. 12. Section showing an epi-myoepithelial island. Of note are the poor definition of cell membranes, the loss of purposeful arrangement, and the two types of cells (see text). × 400.

FIG. 13. Another epi-myoepithelial island showing early hyalinization centrally. × 400.

FIG. 14. Epi-myoepithelial island showing duct-like structures and hyalin. × 400.

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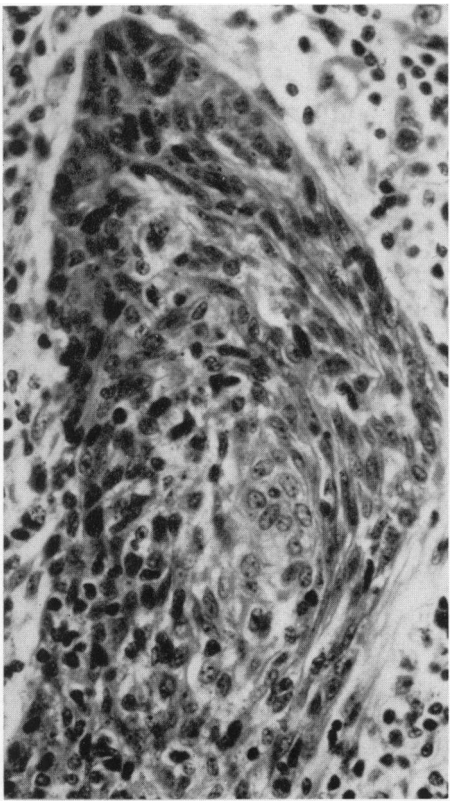

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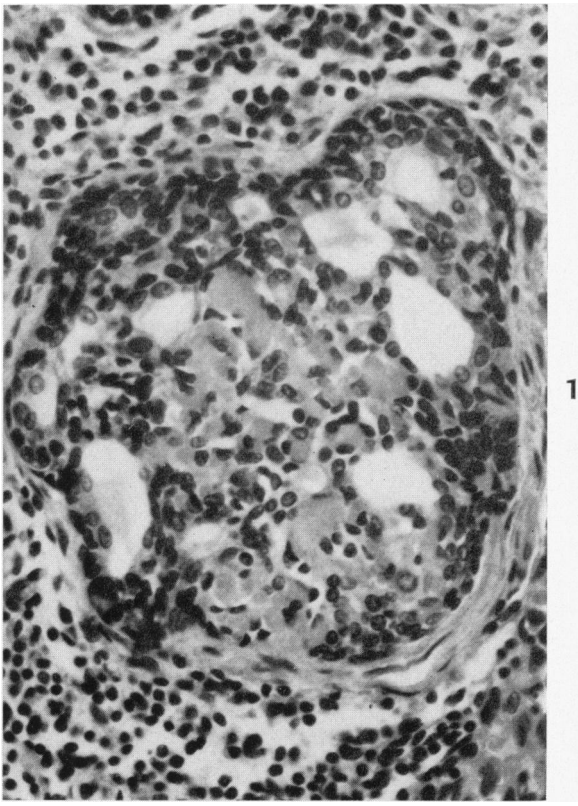

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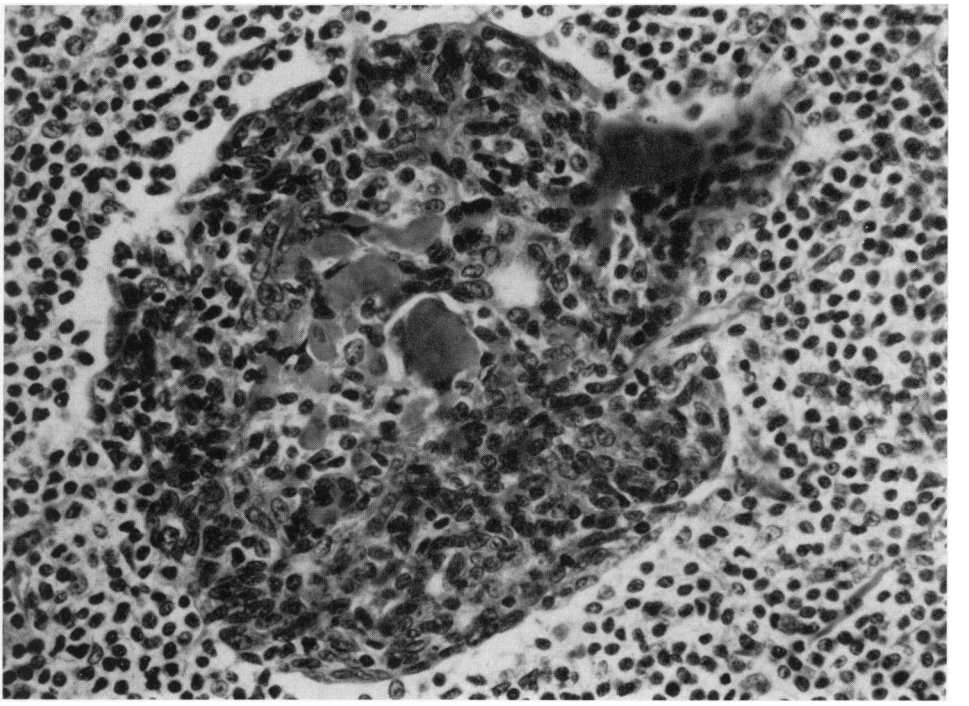
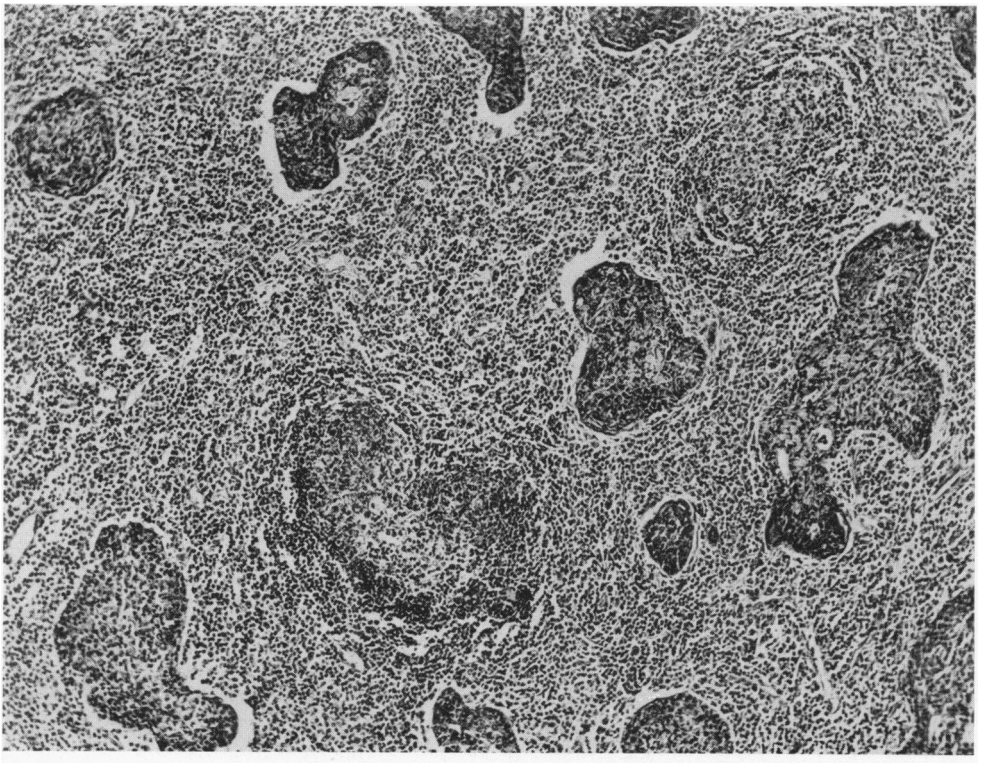


FIG. 15. Area showing scattered epi-myoepithelial islands in a lymphoid stroma. × 180.

FIG. 16. A Foot stain showing the fine background of reticulum in the stroma and the preservation of basement membrane in an epi-myoepithelial island. × 180.

FIG. 17. Chronic sialadenitis. An example of the type of lesion ordinarily seen in duct obstruction. × 180.

FIG. 18. Chronic sialadenitis showing the typical appearance of the ducts in this condition. Dilatation of the lumen and flattening of the ductal epithelium are in contrast to the lesion described in Mikulicz's disease. × 400.



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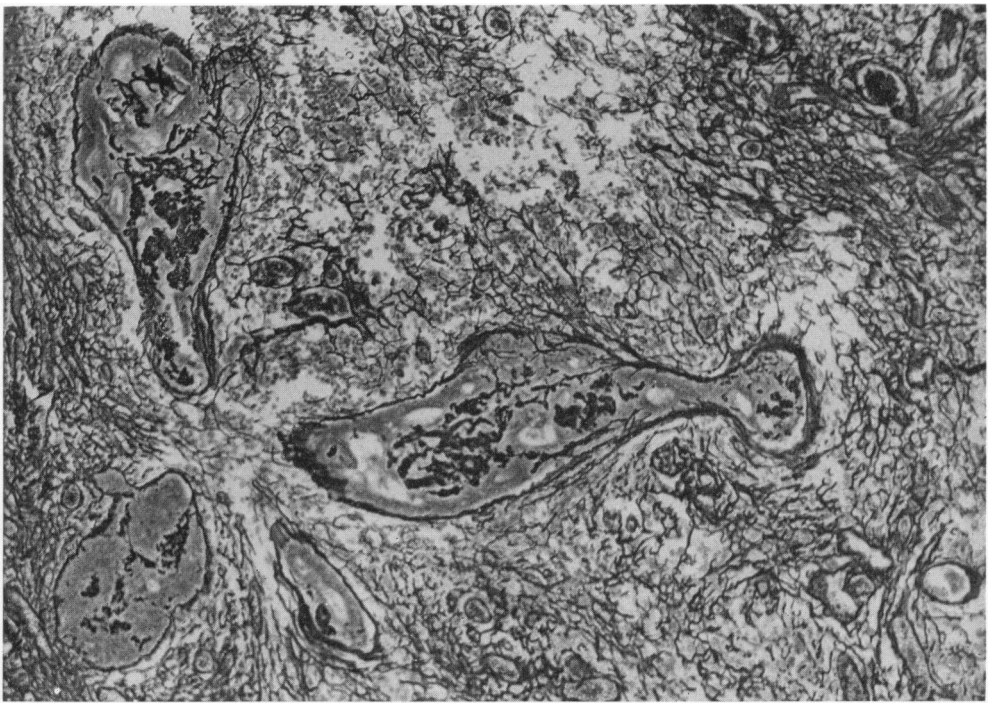

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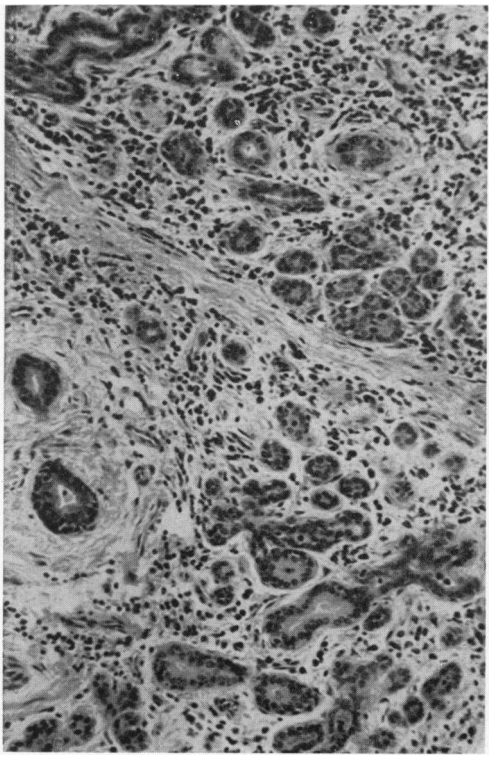

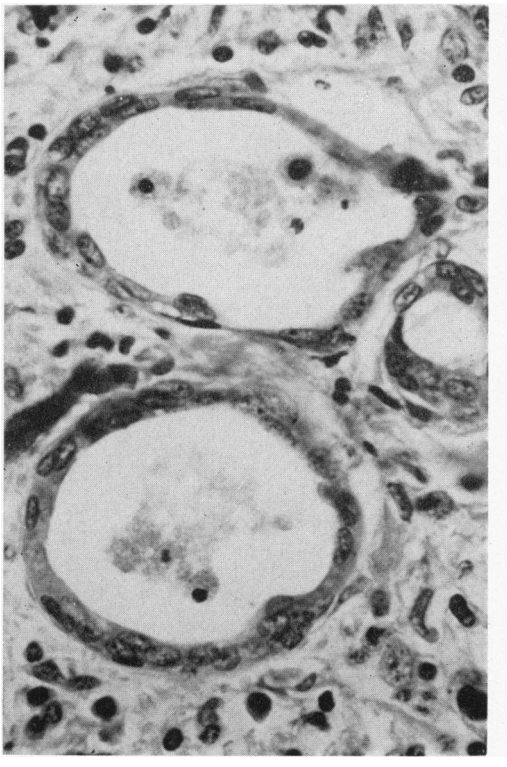

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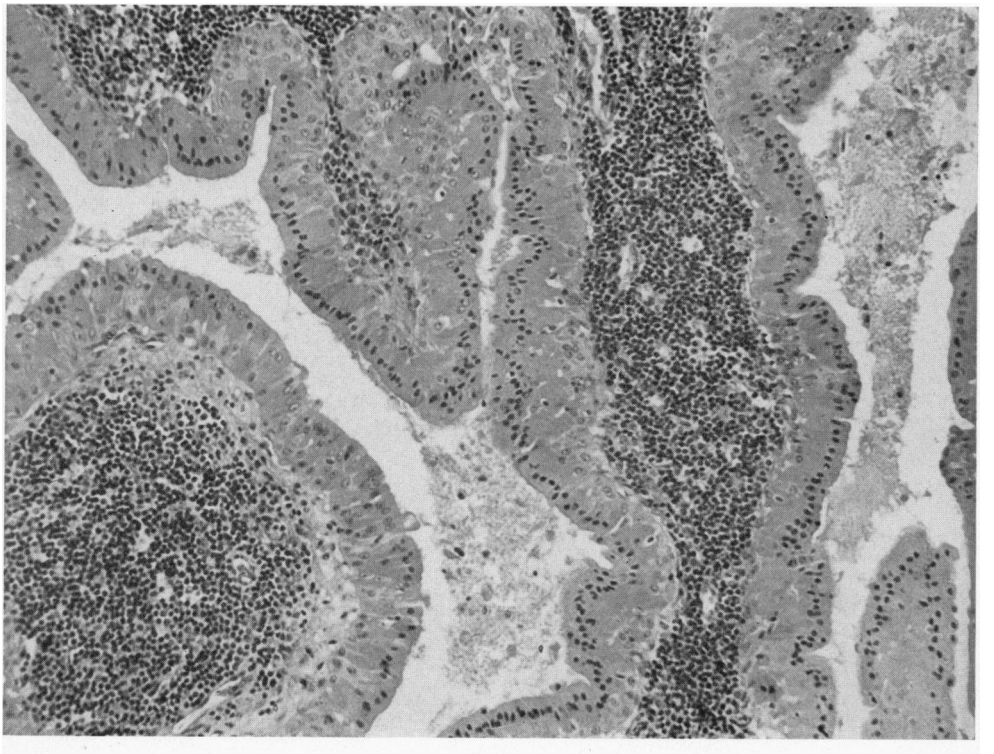
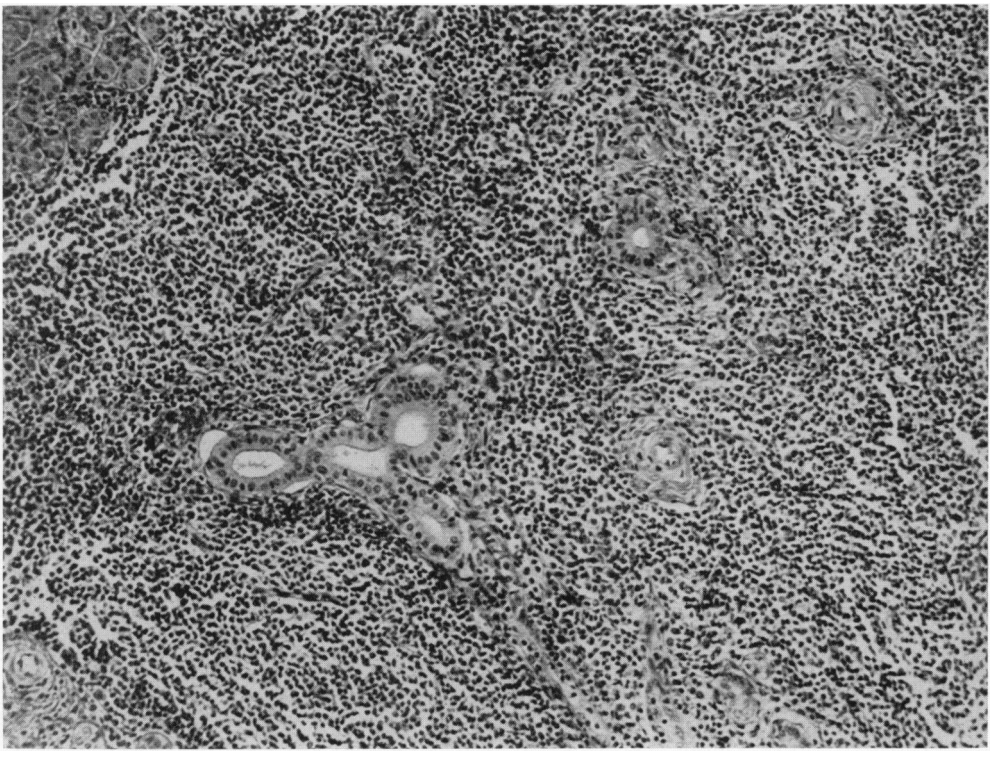
FIG. 19. Papillary adenocystoma lymphomatosum (Warthin's tumor). × 180.

FIG. 20. Malignant lymphoma of the salivary gland. Normal appearing ducts are present, epi-myoepithelial islands are absent. × 180.

FIG. 21. Malignant lymphoma of the salivary gland. Another example showing atrophy of the ducts but no epi-myoepithelial islands. × 180.





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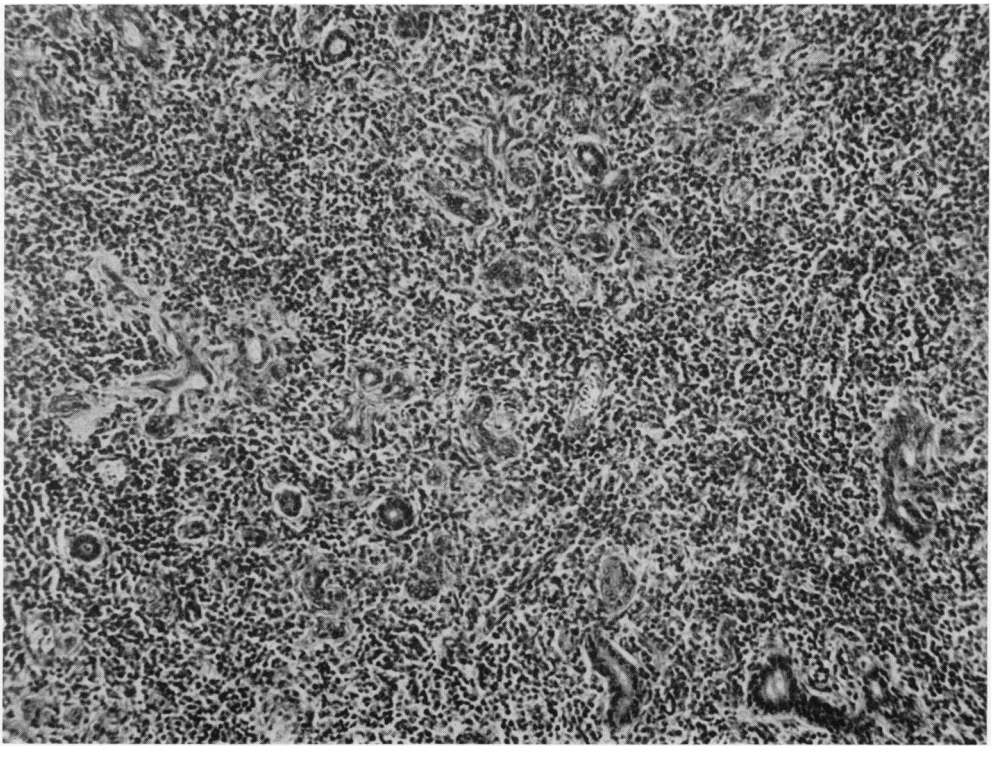

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