THE PROBLEM OF MIKULICZ'S DISEASE

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'I hope that future observers will succeed in solving the riddle which this remarkable disease presents to us.'

von Mikulicz, 1888.

In 1888 von Mikulicz[41] described a patient who had enlargement of the lacrimal and salivary glands. The one lacrimal gland was excised and the histology showed lymphoid infiltration with acinar atrophy.[23] The enlargement recurred and it was again excised but the patient died 2 months later from peritonitis originating in perityphlitis. This unhappy end occurred 14 months after the onset of the disease.[14, 17] What von Mikulicz described is as unknown today as it was then[11] and in view of the early death of the patient it is even impossible to say whether his patient was suffering from a benign or a malignant condition.

After that original report considerable confusion was caused by the fact that all types of cases with similar swellings were labelled as Mikulicz's disease.[16] In an attempt to restore order out of the resultant chaos, it was suggested that the term Mikulicz's syndrome should be used for those cases resembling von Mikulicz's original case but caused by some known disease[12, 20, 28, 29] such as tuberculosis, leukaemia,[12, 14]

lymphomata,[12, 21] syphilis,[14] sarcoidosis[14] and uveoparotid fever[12, 13, 35] (which is, in fact, also sarcoidosis.[14]) The diagnosis of Mikulicz's disease should then be reserved for those benign cases without any known cause.[1, 14, 23, 32, 33, 42]

THE CLINICAL PICTURE

Mikulicz's disease is a rare condition and, in a series of over 200 patients with swelling of the parotid salivary gland, one has encountered only 3 cases.

Racial Incidence. There is no information available about the racial distribution of this condition but it is possibly significant that all 3 of my cases occurred in White people, even though half of the patients with parotid enlargements were non-Whites.

Sex Incidence. All 3 patients were females. A marked predominance of females has been reported before;[8, 9, 24] its significance is as yet obscure although it naturally raises the question of some hormonal aetiology.

Age Distribution. Although there is a wide variation, this condition is particularly common in middle age,[9, 24] with an average age of 35.[33] My 3 patients were 18, 22 and 38 years of age.

The Parotid Gland. The usual history obtained is one of slowly progressive enlargement of the parotid salivary gland for weeks, months or even years.[26, 38] One or both glands may be involved,[9, 38] and the whole or only part of the gland may be affected.[8, 11, 30] At the beginning the swelling is rubbery in consistency but it becomes harder as the disease progresses.[26]

The 3 patients reported here illustrated all these classical points. The one showed involvement of a portion of the one gland only, another had enlargement of one whole gland and the third had diffuse involvement of both glands. The latter patient had been affected for 18 months only and the swellings were lobulated and rubbery in consistency, but the other two, who had been affected for 3 and 5 years respectively, had very hard glands, closely simulating a neoplasm.

Pain is usually absent and if present it is absolutely minimal.[26] This has been my experience too. Two patients had no pain at all, but the third had occasional very slight pain and 3 years after the commencement of the swelling she developed a dull, gnawing pain with occasional exacerbations at odd intervals, unrelated to meals.

The Parotid Duct, Duct Orifice and Saliva. These are always normal in this disease, but late in the disorder the affected gland will secrete very little saliva indeed. It is sometimes stated that the patients complain of a dry mouth; this should not occur, because the remaining salivary glands are still normal and should be sufficient to keep the mouth lubricated. The reported cases of a dry mouth are instances of Sjögren's syndrome, which should not be confused with Mikulicz's disease.

The Lacrimal Glands. Von Mikulicz's original case had lacrimal-gland enlargement, but as has been pointed out there is complete uncertainty about the nature of the condition he reported; it may well have been one of the conditions now grouped under the term Mikulicz's syndrome, in many of which lacrimal enlargement commonly occurs. So the fact that von Mikulicz's patient had enlargement of the lacrimal glands does not mean that lacrimal gland enlargement should be present in the disease which now carries his name.

If all cases of Mikulicz's syndrome are excluded, it is found that lacrimal enlargement is not a feature of Mikulicz's disease.[11, 26] None of the 3 patients here reported had enlargement of the lacrimal glands, although this has been seen in Mikulicz's syndrome produced by a lymphoma. It is thus difficult to evaluate reports of cases with lacrimal-gland enlargement in Mikulicz's disease,[23, 24] for one is never sure that the authors appreciate the fact that Mikulicz's disease is a separate entity.

MACROSCOPIC AND HISTOLOGICAL APPEARANCES

Macroscopic

The whole or part of the gland may be affected. The normal lobular structure is retained[24] and the increase in the fibrous tissue in the trabeculations accentuate the lobulations of the gland.

The cut surface is greyish white,[8] unlike the yellow colour of the normal gland. Occasionally an area resembling a chronic abscess is seen and in two of my patients such a cavity was encountered.

Histology

All 3 cases were examined histologically and in 1 case one was fortunate to obtain sections soon after the onset of the disease, again 1 year later, and again 3 years later, thus enabling one to follow the progress of the disease.

At the onset it seems as if there is an inflammatory response in the septa of the gland,[39] which results in an increase in the fibrous tissue of the trabeculae separating the lobules from each other (Fig. 1).

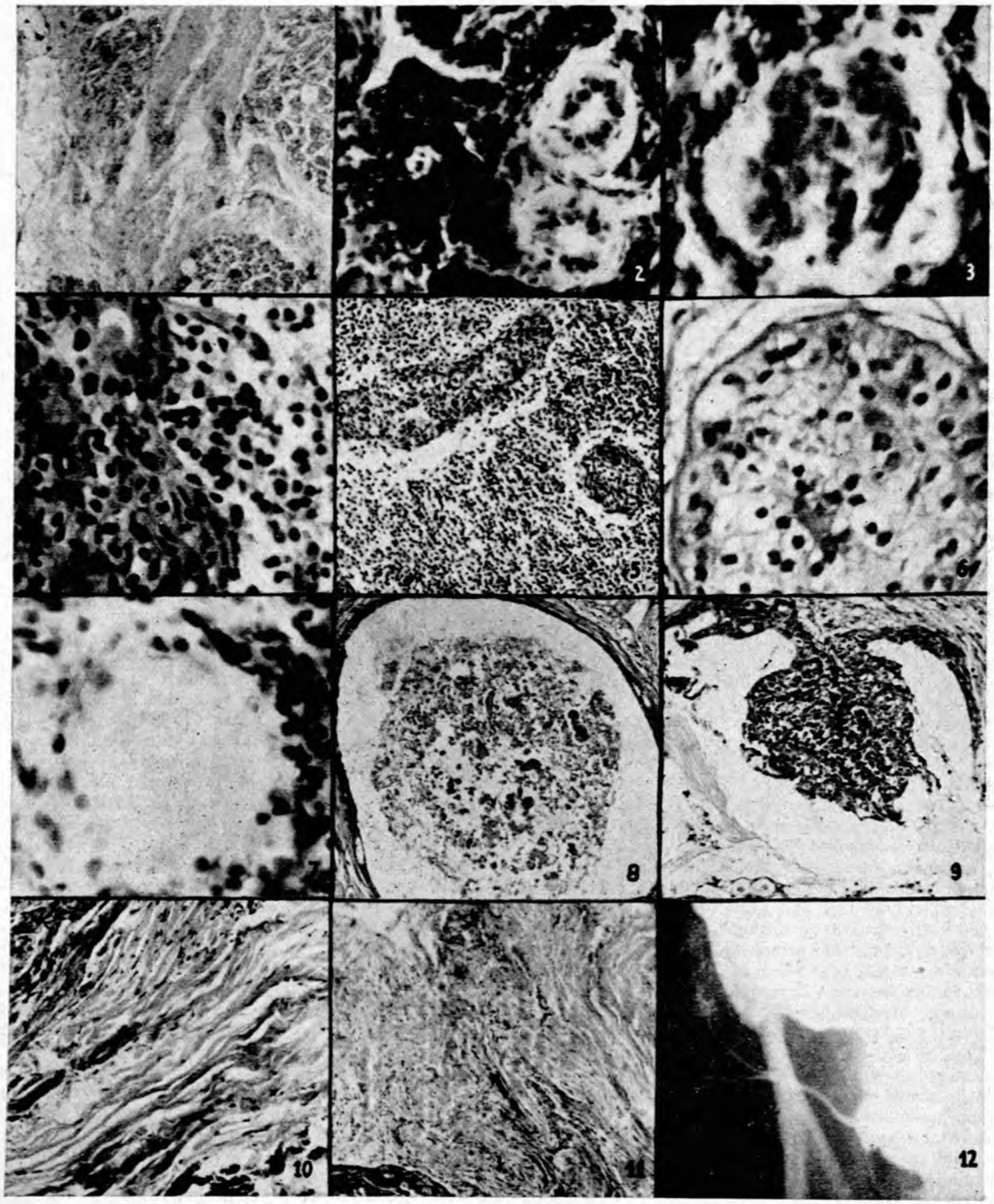
Later the process spreads to the gland parenchyma, the degree of change depending on the duration of the disease. Here the striking feature is a lymphocytic infiltration which commences around the intra-lobular ducts (Fig. 2).

The epithelium of these intra-lobular ducts soon show hyperplasia of the epithelial and myo-epithelial cells normally present in the duct;[24, 43] the epithelial cells have large ovoid, circular or reniform nuclei, while the myo-epithelial cells are thin and elongated with hyperchromatic spindle-shaped nuclei which are triangular on cross section[24] (Fig. 3). The myo-epithelial cells are also shown up by Masson's erythrosin-saffron stain, which stains the cytoplasm of myo-epithelial cells a bright pink.

At first this epithelial proliferation is confined by the basement membrane of the duct, but there is fragmentation of the reticular and collagenous tissue supporting the duct wall[26] and eventually the cells extend beyond the duct, thus resembling a malignant process (Fig. 4).

After a time the ducts become completely solid cords of cells, forming islands amongst the lymphocytes—the so-called epi-myo-epithelial islands[24] (Fig. 5 and 6). These islands eventually undergo hyaline degeneration, which increases with the duration of the condition, being minimal at 1 year, moderate at 5 years and severe after 10 years, until the whole island is replaced by an acellular acidophilic mass.[24] In one of my cases this was found to be present 3 months after the onset of the disease (Fig. 7).

This epithelial hyperplasia gradually encroaches on the lumen of the duct to produce some obstruction, with dilatation of the ducts distal to it (Fig. 8). The dilated duct may also demonstrate vigorous epithelial activity to produce small excrescences in it[24] (Fig. 9).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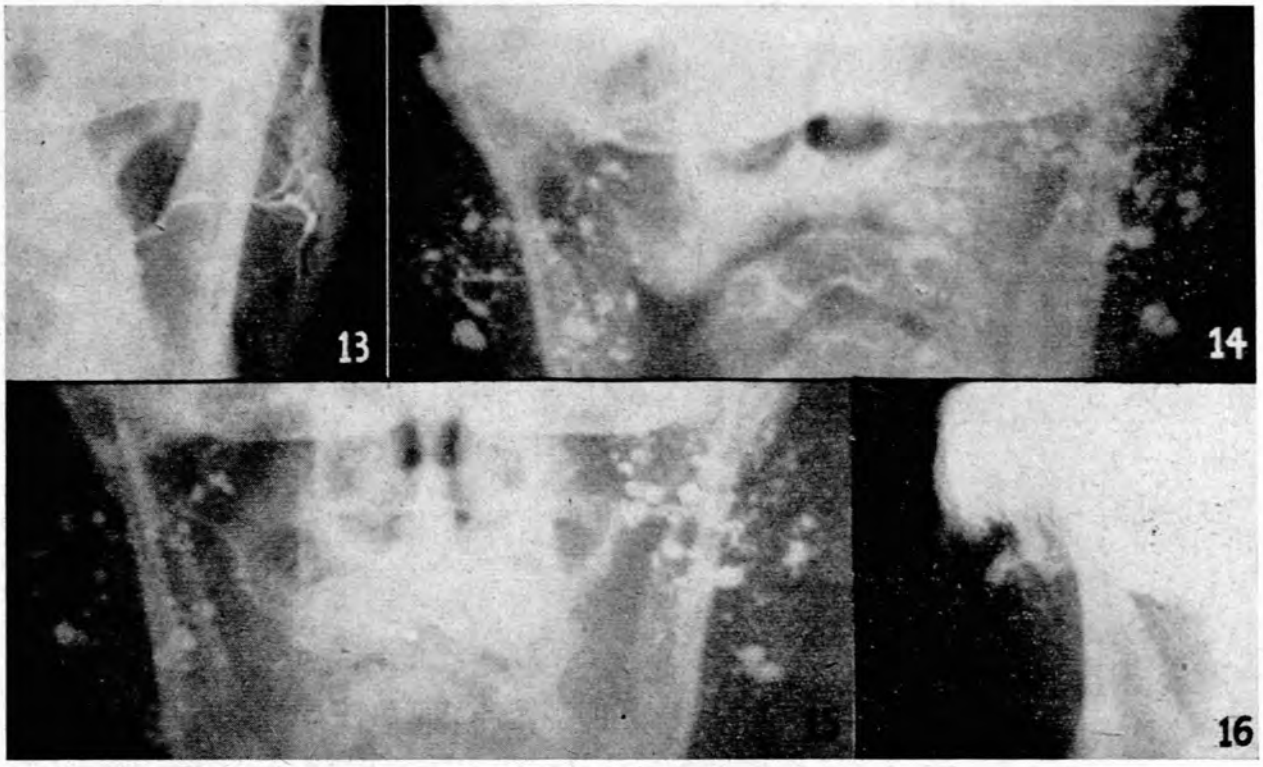
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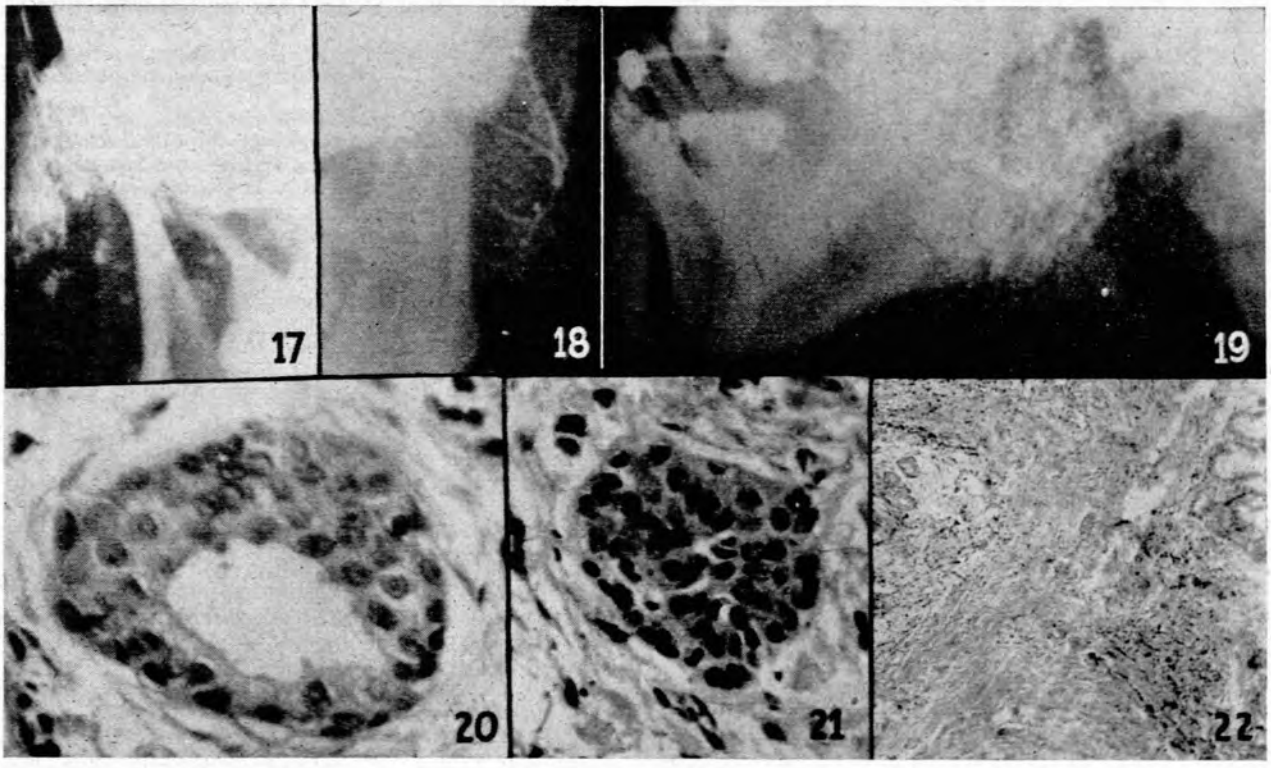
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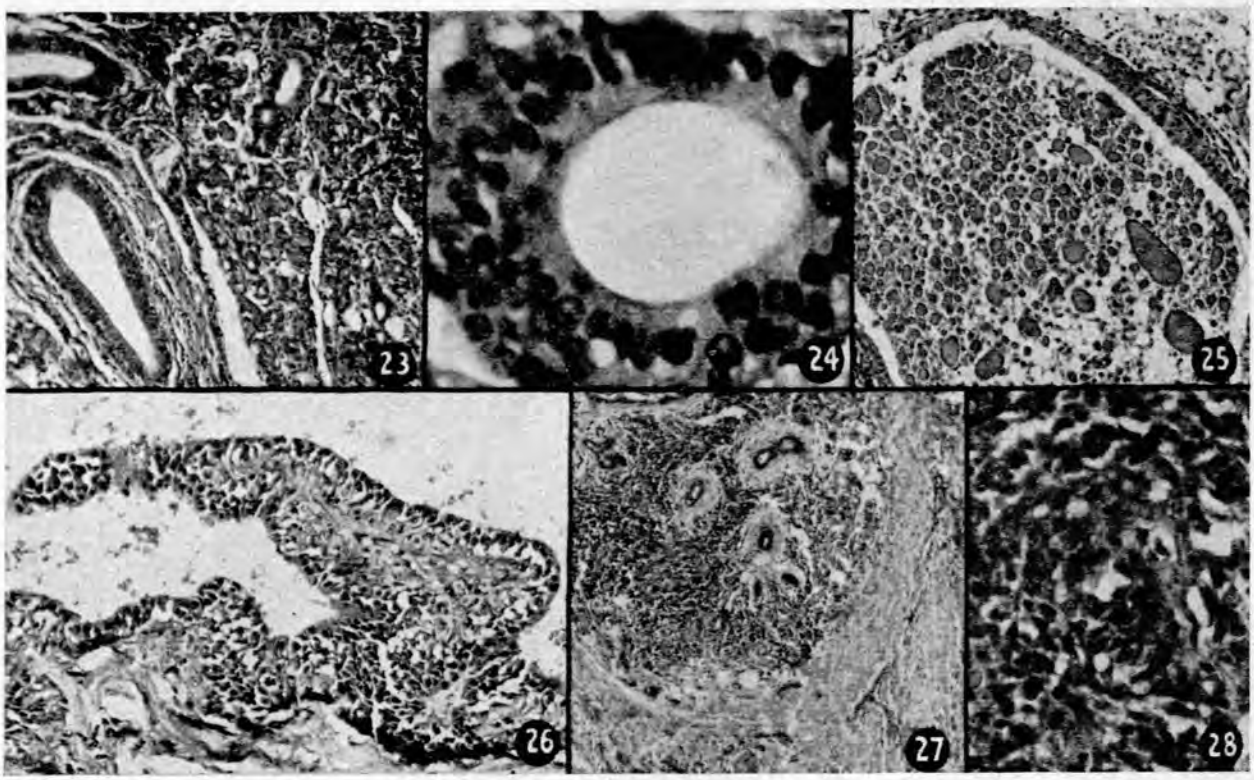

Fig. 1. Increase in fibrous trabeculations in the parotid gland 3 months after the onset of Mikulicz's disease. H. & E.

Fig. 2. Lymphocytic infiltration around the intra-lobular ducts of the parotid gland in Mikulicz's disease. H. & E.

Fig. 3. Poliferation of epithelial and myo-epithelial cells lining the intra-lobular ducts of the parotid gland in Mikulicz's disease. H. &. E.

Fig. 4. Epithelial proliferation beyond the confines of an intralobular duct of the parotid gland in Mikulicz's disease. H. & E.

Fig. 5. Epi-myo-epithelial islands in the parotid gland to Mikulicz's disease. H. & E.

Fig. 6. A higher-power view of an epi-myo-epithelial island in the same gland as in Fig. 5. H. & E.

Fig. 7. Hyaline degeneration in an epi-myo-epithelial island in the parotid gland of Mikulicz's disease. H. & E.

Fig. 8. A dilated duct in the parotid gland of Mikulicz's disease. H. & E.

Fig. 9. Epithelial proliferation into a dilated duct of parotid gland in Mikulicz's disease. H. & E.

Fig. 10. Acinar atrophy and replacement by lymphocytes and fibrous tissue in the parotid gland 15 months after the onset of Mikulicz's disease. H. & E.

Fig. 11. Marked fibrosis in parotid gland 3 years after the onset of Mikulicz's disease. H. & E.

Fig. 12. Sialogram (A.P. view) of a person with Mikulicz's disease, showing obstruction of a main intra-glandular duct.

Fig. 13. Parotid sialogram (A.P. view) in Mikulicz's disease, showing inadequate filling of the finer ductules owing to obstruction of the finer ducts.

Fig. 14. Bilateral parotid sialectasis in a case with Mikulicz's disease.

Fig. 15. Radio-opaque material still present in both glands 5 minutes after Fig. 14 during which time a lemon had been sucked for 1 minute.

Fig. 16. Sialogram taken immediately after the injection of 1·5 ml. Neo-Hydriol fluid in a patient with Mikulicz's disease.

Fig. 17. The same case as Fig. 16 but taken 24 hours later.

Fig. 18. Sialogram of an early case with typical Sjögren's syndrome (before any parotitis).

Fig. 19. Sialogram to show sialectasis in a patient with Sjögren's syndrome after many attacks of parotitis.

Fig. 20. Photomicrograph of a parotid gland after many attacks of parotitis, showing duct epithelial hyperplasia. H. & E.

Fig. 21. Photomicrograph to show a duct solid with proliferating epithelial and myo-epithelial cells in a patient with recurrent parotitis. H. & E.

Fig. 22. Acinar atrophy, lymphocytic infiltration and fibrosis in a patient with recurrent parotitis. H. & E.

Fig. 23. Periductal lymphocytic infiltration in the parotid gland of a patient with duct obstruction. H. & E.

Fig. 24. Hyperplasia of cells lining a duct in a case of parotid-duct obstruction. H. & E.

Fig. 25. A dilated duct in the parotid gland of a patient with parotid-duct obstruction. H. & E.

Fig. 26. Proliferation of epithelial cells into a dilated duct of a patient with parotid-duct obstruction. H. & E.

Fig. 27. Photomicrograph of a submandibular gland after many attacks of inflammation, showing interlobular fibrosis, acinar atrophy, and periductal lymphocytic infiltration. H. & E.

Fig. 28. Duct epithelial hyperplasia and lymphocytic infiltration in the same gland as in Fig. 27. H. & E.

While this process develops, there is a well-marked atrophy of the acini; it is uncertain why this takes place but it is tempting to postulate that it is a result of duct obstruction. As the acini disappear they are replaced by lymphocytes and fibrous tissue (Fig. 10).

The end result is a hard gland consisting almost entirely of fibrous tissue (Fig. 11), and in my own experience it is only at this stage that pain becomes a feature of the disease.

SIALOGRAPHIC APPEARANCE

As can be expected, duct obstruction with failure to fill the ducts and gland beyond the obstruction will constitute a striking feature of this condition. In one case there is obstruction of a major duct (Fig. 12), possibly due to the fibrosis and periductal lymphocytic infiltration in the septa around the inter-lobar ducts.[39] This particular patient had had a biopsy taken by her own doctor some months before and it is possible that the duct obstruction was a sequel of this operation; but it is unlikely that the biopsy was taken so deeply, and no salivary fistula followed that operation, which one would have expected if there had been damage to such a large duct.

In the second case this duct obstruction occurred in the terminal ducts, resulting in areas which failed to fill adequately (Fig. 13).

The classical sialographic appearance is that of sialectasis (Fig. 14). It has usually been assumed that sialectasis is produced by the pooling of radio-opaque material in dilated ducts, but it is in fact due to extravasation of the injected material out of the abnormally weak ductules into the interstitial tissue of the gland.[26] This view is supported by the following findings:

(i) Histologically such enormously dilated ducts are not seen.

(ii) The radio-opaque material does not leave the gland after sucking a lemon for 1 minute and taking another plate 5 minutes later (Fig. 15). In other conditions where the dye is lying in the ducts it becomes washed out by the salivary flow stimulated by sucking a lemon, as can be seen in mixed salivary tumours, in congenital sialectasis, and even in obstructions of the parotid duct.

(iii) In other parotid glands, if 1·5 ml. of dye is injected it produces acinar filling which empties very readily after sucking a lemon. In one of my patients described here, however, the injection of 1·5 ml. of dye resulted in extravasation of the injected material into the interstitial tissues of the gland and from there it spread inside the confines of the parotid fascia, as can be seen in plates taken immediately after the injection (Fig. 16), and again 24 hours after the injection (Fig. 17).

It thus seems likely that in this condition there is an abnormal weakness of the intra-glandular ducts, which rupture and allow extravasation of dye much more readily than normally.

It is obvious that the irritation produced by this extravasation of dye will aggravate the fibrosis of this disease, and sialography should thus be done very gently.

THE NATURE OF MIKULICZ'S DISEASE

It is often stated that Mikulicz's disease and Sjögren's syndrome are the same condition,[1, 24, 39] the former being merely a less highly developed variant of the latter.[23] This view is based on the fact that the sialographic and histological appearances are very similar in the two conditions. Personally I do not hold that view; I consider Sjögren's syndrome to be primarily a condition of impaired secretion of various glands, including the salivary glands. This produces all the manifestations of the so-called sicca syndrome. The resultant dry mouth and poor salivary flow produces attacks of parotitis, and it is these attacks which produce the typical radiological and histological features. This view is based on several facts:

(i) In the early stages of Sjögren's syndrome the sialogram is normal, as can be seen in Fig. 18, from a patient with the typical sicca syndrome. Sialectasis is only seen after repeated attacks of acute parotitis, as can be seen on the plates of such a patient (Fig. 19). These plates are in no way different from those seen in any other type of recurrent parotitis.

(ii) The typical histological picture of Mikulicz's disease has been reproduced experimentally by producing obstruction and by inducing infection in the gland.[3]

(iii) Early in Sjögren's syndrome there is only glandular atrophy,[5, 6] and the typical appearance histologically is the result of the recurrent attacks of parotitis.[6]

(iv) The histological features of Mikulicz's disease is also found in recurrent parotitis and in pure duct obstruction. Thus in recurrent parotitis with sialectasis one can see duct epithelial hyperplasia (Fig. 20) with the formation of solid ducts (Fig. 21) and eventually fibrosis and acinar atrophy with lymphocytic infiltration (Fig. 22). Similarly, in a case with duct obstruction there was lymphocytic infiltration (Fig. 23), duct epithelial proliferation (Fig. 24), dilated ducts (Fig. 25) with excrescences into them (Fig. 26).

It is thus obvious that this histological picture of acinar atrophy, proliferation of duct epithelium, lymphocytic infiltration and fibrosis is not pathognomonic of any one disease, and I suggest that it is a non-specific reaction on the part of the parotid to chronic irritation,[11] whatever the cause of the irritation. This same histological picture may even be seen in the submandibular salivary gland which has been subjected to recurrent attacks of infection (Figs. 27 and 28).

The diagnosis of Mikulicz's disease must thus not be made on the basis of the histological picture alone, as is so frequently done,[39] but on the combination of the clinical picture, sialography and histology. If these strict criteria are used in the diagnosis of Mikulicz's disease it will not be confused with Sjögren's syndrome and it will be found that many cases reported in the literature as cases of Mikulicz's disease are in fact some other condition, notably recurrent parotitis whether due to Sjögren's syndrome or not.

It is as yet uncertain what the cause of the chronic irritation is in Mikulicz's disease. It may be exogenous or endogenous.[2] Of the exogenous causes, infection is the one most frequently suggested,[11, 32] but no organism has ever been found in these cases and in my own cases the saliva has been sterile. In one case the contents of a cavity found in the centre of the mass at operation was also sterile on culture. In the patient with the bilateral swellings a cystic mass appeared on the one side 6 months after the biopsy and 3 months after the small dose of deep X-ray therapy. Aspiration revealed a thick fluid which was sterile on culture and consisted of necrotic material only. It had a salivary-amylase content of 100 units per ml.

All this strongly suggests that Mikulicz's disease is not due to a bacterial infection but it does not, of course, rule out a virus infection. This is now being investigated, because

there is ample evidence of viruses infecting the parotid gland in other conditions such as mumps, cytomegalic inclusion disease[44] and, more recently, in association with herpangina.[45] Dr. A. Kipps very kindly investigated the fluid aspirated from the cyst in the gland of the one patient described above. No virus was found in the fluid. This one case still does not exclude a virus as the causation, of course, more especially as this patient had received deep X-ray therapy before the fluid was aspirated.

Of the endogenous causes, it has been suggested that it may be one of the connective-tissue diseases in view of an association with disseminated lupus erythematosus;[23] but this has not been confirmed.

A most tempting suggestion is that there is an increased permeability of the intra-glandular ducts,[24] and that this allows saliva to escape into the interstitial tissue of the gland to produce the irritation.[26] This is pure hypothesis at present but it would fit in with the disease as we know it. In the hope of finding some auto-sensitivity to saliva in these people, I have investigated one patient fully, with the following findings: White blood count: 8760 per c.mm., polymorphs 62%, lymphocytes 30%, monocytes 2%, eosinophils 6%. Sedimentation rate: 1 mm. in 1 hour. Haemoglobin 15 g.%. Serum albumin 5·5 g.%, serum globulin 2·3 g.%, serum calcium 11 mg.%. Thymol turbidity 4·4. Zinc turbidity 7·4. Alkaline phosphatase 2·6 Bodansky units.

Four weeks after a course of deep X-ray therapy to both the parotid glands, with good effect, the results were: Thymol turbidity 4. Zinc turbidity 2. Serum albumin 4·4 g.%, serum globulin 4·8 g.% (i.e. an increase in total globulin). Electrophoresis showed this increase to be due to an increase in alpha 2 globulin.

Whether the eosinophilia and the increased alpha 2 globulin have any significance is not certain, but there seems little evidence of a sensitivity reaction.

A precipitin test (kindly performed by Dr. A. Kipps) between the patients' serum and a saline extract of another person's parotid gland was also negative.

TREATMENT AND PROGNOSIS

Because its nature is obscure, the treatment we can offer must be empirical.

The management of this condition is largely controlled by the suspicion or fear that it is a neoplasm, and consequently most people will insist on a biopsy before any decision is made regarding treatment.[11, 26]

If the condition is localized, it will resemble a neoplasm so closely that it would be wise to excise the mass without biopsy unless facilities for frozen sections are available. Such an excision was performed on one of the 3 cases here reported and she is well.

If it is a diffuse condition in the relatively early stages with a rubbery consistency (suggesting lymphocytic infiltration without much fibrosis) then deep X-ray therapy in small doses may be most effective.[8, 9, 11, 14, 16, 17] This was used in my one patient with bilateral parotid involvement, who was given the equivalent of 850 r total to each side with a remarkably satisfactory result.

In the later stages, when the gland is hard owing to fibrosis, parotidectomy should be performed (with preservation of the facial nerve) if the symptoms (pain or disfigurement) warrant it.[26, 38] This was done on one of my patients with a satisfactory result.

Prognosis. There is no mortality associated with this disease and the prognosis must thus be said to be good.[9] The local mass may disappear with radiotherapy; if not, parotidectomy will remove it successfully. Recurrences, however, do occur,[11] or, in some cases, the opposite side may become affected.[11]

CONCLUSIONS

Mikulicz's disease should thus be diagnosed on the basis of the clinical, sialographic and histological pictures taken together because the sialographic appearance is not pathognomonic and the histological features are those of a non-specific response to chronic irritation.

The aetiological factor responsible for this condition is as yet obscure, but two aspects are being investigated: the possibility of a virus infection and the interesting theory that it may be due to a sensitivity of the gland to some constituent in the saliva.

It remains only to consider whether we should continue calling this condition Mikulicz's disease. The name has the advantage that it is a generally known term but the objections are that it may become confused with Mikulicz's syndrome and that there is no proof that the case von Mikulicz originally described was in fact the condition we are discussing.

One thus feels that the term should be abandoned; the difficulty, however, is to find a suitable substitute. Various names have been proposed but they all have their objections; e.g. benign lympho-epithelial disease[11] (apt to be confused with lympho-epithelioma), lymphocytic tumour[18] (but it is not a tumour in the common usage of the term), chronic sialectatic parotitis[26] (but true sialectasis is not present), adenolymphoma[15, 19, 27] (but we reserve that name for a very specific condition[42]). It certainly seems like an inflammatory response to an irritant which is as yet undetermined, and it would thus seem to be logical to call the condition idiopathic chronic parotitis.

SUMMARY

Mikulicz's syndrome must be clearly distinguished from Mikulicz's disease.

The histological picture of Mikulicz's disease is acinar atrophy, periductal lymphocytic infiltration, duct-epithelium proliferation and fibrosis. This is not specific for this condition but is a non-specific response on the part of the parotid gland to any chronic irritation. It is even seen in the submandibular salivary gland after recurrent attacks of inflammation.

A better name for this condition is Idiopathic Chronic Parotitis.

The various sialographic appearances of this disease are described; none of them are pathognomonic.

This condition can thus only be diagnosed by a consideration of the clinical, sialographic and histological pictures.

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