THE MIKULICZ SYNDROME

WITH

NOTES OF FIVE CASES.

THESIS

Submitted for the

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by

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INTRODUCTION.

The origin of the research on the material for this thesis was the occurrence in the course of the writer's practice of a case (case 1) which corresponded in the details to the case of Bilateral salivary and lachrymal gland enlargement, first described by Mikulicz: (1.) Details of two other cases, hitherto unpublished and which occurred in the same neighbourhood, were mentioned to the writer and the medical men who had observed them, gladly gave their assistance in the way of clinical notes (cases 2 & 3) and photographs, (case 3.)

A fourth case published in full was studied, and permission to use the notes and photographs was freely conceded. Many enquiries were sent out, and all received favourable notice from the recipients. In one case, a patient who had been observed some years previously whilst suffering from the condition, was examined to ascertain the progress of the disease and the present state of health of the patient. (Case 2.)

The disease is a rare one, and the average standard, popular text-book, both of Medicine (2,3,4,5 & 6)
and Pathology (7, 8 & 9) have singularly little to say about the condition, and one needs to search well into the Medical Journals to find recorded cases. A fact which strikes one is that the larger proportion of the literature has been contributed by German workers, and only latterly has there occurred more frequent references in British and American literature.

There is not enough, therefore, in the usual sources of information in a form for easy reference, to satisfy one who is faced with a case in the course of his practice and who has to be able to prescribe treatment, give a prognosis and talk intelligently about the condition to patient and relatives, who seem nowadays to be of a particularly enquiring turn of mind.

The case actually under the writer's immediate observation and care has been investigated with regard to blood picture and pathology of the tumour mass in the conjunctiva. Certain changes in the appearance of the condition have been observed and a very definite improvement, with complete and rapid disappearance of the tumour under certain prescribed treatment, has been noted.
Other cases extracted from the literature are discussed and compared, the various types of pathology encountered, methods of treatment and results noted.

The main object of the present thesis, is to discuss whether "Mikulicz Disease" can be considered a clinical entity or merely a symptom complex or syndrome, to find out the pathology of the condition and to review methods of treatment and, lastly, to make clear that point, which is to the patient the most important of all, the prognosis.

With these points in view it is intended that the title of this contribution to the study of the condition, be - "Mikulicz Syndrome, With Notes on Cases Observed."
Attention was first called to the condition at present under discussion by Johann Von Mikulicz-Radecki, a distinguished Polish surgeon, (1850-1905) who has had the doubtful honour paid to him of having this pathological condition bear his name. In 1888, he showed before the "Verein für Wissenschaftliche Heilkunde" at Konigsberg, where he was a professor of surgery, a case of enlargement of the lachrymal and salivary glands. In view of its historical importance, I take the liberty of introducing here an abstract of the notes of the case which he described.

"January 13th, 1888. The patient was a powerfully built, well nourished man of otherwise healthy appearance. Nothing abnormal was found in the internal organs. No albuminuria. No enlarged glands found elsewhere. The blood showed no special changes. Pulse and temperature normal. The face was extraordinarily altered in appearance by symmetrical swellings in the neighbourhood of the upper eyelids, and of the parotid and submaxillary glands. The orbital fissures were narrowed to small triangular fissures, the base of which was formed by the inner two-thirds of the edge of the lower lid. A certain amount of convergent strabismus has resulted from this condition. There was slight salivation, dysarthria and dysphagia.
On palpation, a small, knobby, dense tumour of transversely oval shape, was found under the outer half of each upper eyelid. The conjunctiva itself was slightly reddened and a little thickened. The sight was unaffected. In the parotid area on both sides there was a flattish, not very prominent, and uniform tumour, extending forwards to the middle of the cheek, backwards to the mastoid process, and so lifting the lobule of the ear considerably. In each submaxillary region there was a tumour about as long as a hen's egg of dense consistency, and slightly movable. The two tumours almost met in the middle line under the chin. On opening the patient's mouth the sublingual glands presented as two elongated swellings about the shape and size of an almond set on its edge, and occupying the floor of the mouth on both sides of the frenum linguae. The glands of the soft palate exhibited an enormous increase in size, forming a sharply defined tumour as big as a chestnut on both sides, and being separated by a groove 0.5 cm. wide in the middle line. During the examination of the patient there was a free secretion of saliva, though there was no appearance of a flow.

As the swelling of the eyelids was the only thing which caused the patient much discomfort, a partial removal of the enlarged lachrymal glands was undertaken on February 1st., 1888. On either side, a mass of tumour about 2.5 cm. long by 1.5 cm. broad, was removed. Healing was normal, and the patient left the hospital in a few days, well pleased with the result. The improvement was, however, very transient; the swelling of the upper eyelids speedily recurred, and the patient returned to hospital at the end of March, the swelling of the lachrymal glands being then nearly as large as before the operation. Pilocarpine was injected in the hope that an increased secretion might reduce the size of the glands. No benefit resulted, and on April 19th. the right, and on May 1st. the left, lachrymal gland was extirpated. The patient made an excellent recovery, and was discharged ten days later.

He wrote on July 12th., 1888, that he was well
pleased with his condition, and that he had no trouble with his eyes. The parotid glands appear to have gone on increasing in size, but they did not bother him. He died of perityphlitis early in August, 1888, after nine days' illness. During his illness the parotids rapidly diminished in size, and at the time of his death were almost normal.

Microscopical examination of the lachrymal glands removed by operation showed that the proper gland parenchyma played a purely passive part, and that the increase in size was due entirely to a voluminous infiltration of the interstitial connective tissue by small round cells (lymphocytes).

It will be noted that the lachrymal and salivary glands were the only structures affected, that there were no blood changes and that the principal symptoms came from the mechanical interference due to the enlarged glands. This case was not actually published in any journal until 1892. In the meantime Haltenhoff, in Brussels, had published in 1889 - apparently without having heard of the case shown at Konigsberg - notes of a case of a girl 12 years of age.

Following these many more cases began to be reported, some with involvement of both lachrymal and salivary glands and some with only lachrymal or salivary gland enlargement, or even with enlargement of only one gland. Previous to 1888, there had been published cases of enlargement of lachrymal glands and all these cases began to be
grouped together under the heading of Mikulicz Disease. Certain writers referred to these incomplete forms as "formes frustes" and likened them to the cases which occur in other conditions, such as Myxoedema and Tetany, in which the full clinical picture does not develop but yet one is quite justified in classing such cases under the heading appropriate to them.

Von Brunn, in reviewing the already published work attempted to classify the various types that had been noted, and produced a classification which includes all the types met with up to that time. This classification was as given on page 8. Later, Campbell Howard suggested a simple yet fairly comprehensive classification under these headings:—

(1) Mikulicz Disease proper; in which he included all simple enlargement of lachrymal and/or Salivary Glands without any blood changes.

(2) Cases of Pseudo Leukaemia.

(3) Cases of Leukaemia.

A third classification was suggested in 1927, by Schaffer and Jacobsen which differs somewhat in its outline from the two foregoing, and which is set out as follows:—

(1) Mikulicz Disease
   (a) Familial
   (b) Mikulicz Disease proper.
WITHOUT BLOOD ALTERATION.

- WITHOUT SPLEEN OR LYMPH GLAND ENLARGEMENT.
  - WITH SWELLING OF SPLEEN OR LYMPH GLANDS.
    - LACRIMAL GLANDS
    - SALIVARY GLANDS
        - SYMMETRICAL SWELLING OF LACRIMAL AND SALIVARY GLANDS.
        - WITH SKIN INFILTRATION.

WITH BLOOD ALTERATION.

- SEVERE ANAEMIA WITH LYMPHATIC PSUEDO LEUKAEMIA AND APLASIA OF BONE MARROW
  - LEUKAEMIA
Mikulicz syndrome
(a) Leukaemia.
(b) Tuberculosis.
(c) Syphilis.
(d) Lymphosarcoma.
(e) Toxic: (1) Lead. (2) Iodides.
(f) Gout.
(g) Febris Uveo-parodiidea subchronica

Additional cases are still occasionally being recorded, and doubtless many cases have remained unpublished. Details of various methods of treatment have also been discussed and a review of these, as well as other matters brought to light in the various reports, will be set out in the following pages.
PATHOLOGY.

The obvious pathological lesions in Mikulicz Disease are the enlarged Salivary and Lachrymal glands, and perhaps a brief consideration of these with regard to their normal histology, relation and development, might give some help in understanding their morbid histology.

The Salivary and Lachrymal glands are very similar in their minute structure,\textsuperscript{19a} and they are morphologically identical.\textsuperscript{20} The interstitial tissue of these glands contains abundant lymphoid tissue.\textsuperscript{21}

The Salivary glands consist of the parotid, sublingual, submaxillary and accessory glands in the palate, lips cheek and tongue. These develop as outgrowths from the epithelial lining of the mouth\textsuperscript{19b} and they secrete a mildly alkaline fluid of which the principal constituents are mucin and enzymes.\textsuperscript{22}

In the case of the Lachrymal glands, these are formed as ectodermal invaginations from the region forming the conjunctiva.\textsuperscript{23} They consist of the Lachrymal glands proper and the accessory Lachrymal glands of Krause and
Wolfring, and the glands of the plica and caruncle. These accessory Lachrymal glands have all the same structures as the Lachrymal glands proper, though on a smaller scale.\textsuperscript{23}

The secretion is a slightly alkaline fluid containing sodium chloride as the chief constituent.\textsuperscript{20b}

It will be seen then that morphologically the glands are very similar though apparently, as will be noted later, the normal histology is markedly altered in the pathological processes found in the various cases of Mikulicz Disease studied.

In Milulicz's own case\textsuperscript{1} the Lachrymal gland was excised, and under microscopic examination it revealed that the gland parenchyma proper played purely a passive part in the enlargement and that the increase in size was due entirely to a massive infiltration of the interstitial connective tissue by small round cells. The administration (previous to excision) of pilocarpine in order to stimulate a free flow of Lachrymal secretion in the hope that thereby the swelling of the glands might be reduced, did not have any effect.

Previous to Mikulicz, enlargement of the Lachrymal glands had been reported by Berlin,\textsuperscript{12} (two cases) in
L  LACHRYMAL GLAND.
K  GLANDS OF KRAUSE.
W  GLANDS OF WOLFRING.
H  GLANDS OF HENLE.
M  GLANDS OF MANZ.
S.F  SUPERIOR FORNIX.
I.F  INFERIOR FORNIX.
which microscopic examination of the portions of excised gland showed there was increase in the fibrous connective tissue and small round cells, with here and there remains of gland acini. Power\textsuperscript{13} on the other hand merely reported increase of fibrous tissue with no alteration of glandular substance in the case of hypertrophy of the Lachrymal glands.

Since this, a large number of cases have been described and included under the classification of Mikulicz Disease. In some of these no pathological examination has been made but in many cases glands, or portions of glands, have been available either from biopsy or autopsy, and thus a fairly good number of reports on the pathological structure of the enlarged glands may be studied. For the purposes of the present thesis, reports of one hundred and seventy published cases have been studied and in seventy-two of these there has been a report on the structure of the morbid tissue.

In those cases of congenital or familial enlargement\textsuperscript{24,25,26} that have been reported, no description of the pathological nature of the lesion is available.

Tuberculosis\textsuperscript{27 to 34} has been strongly suspected, and
though in some cases evidence has been brought forward which is difficult to refute, the majority of cases do not show evidence to support the view that this infection is the cause of the condition. Indeed, in one series of cases, Syphilis seemed to be associated with it in a surprisingly large percentage, and taking the whole series of cases under review, twenty-three of these were accompanied by Syphilis to and sixteen by Tuberculosis, to whilst another case showed an invasion by both of these infections.

In considering the pathological reports in this series, the large number which stated that there was an increase of small round cells was remarkable, in fact it was the exception to find any other report.

In most, there was some increase of the fibrous tissue elements and absence or evidence of destruction of the glandular structures; in only one case was any note of hypertrophy of the glands, and in this lymphoid elements were reported to be present. Only a small number were reported as sarcomata to and in one case only, was an epithelial tumour responsible for the enlargement. In the majority of cases, therefore, without any obvious
causal factor, the usual changes one finds pathologically, is an increase of the lymphoid elements, either diffuse or in aggregations, and an increase of fibrous tissue; some appear to show diffuse scarring. A certain number have shown definite leukaemic pictures and it has been suggested that many others, especially those associated with groups of enlarged glands with or without enlargement of the spleen, although not showing a leukaemic blood picture, may have been due to leukaemia and have been observed during an aleukaemic phase. We also get granulomatosis of the glands, and Hodgkins disease with enlargement of the Salivary and Lachrymal glands.

In considering the blood picture of the cases under consideration, these seemed to fall into two main groups — that is, those in which blood examinations were reported. These main groups were those cases showing no grossly pathological alterations in the relation of the different blood cells and only a slight indication of anaemia, and those cases showing an increase of white cells chiefly lymphocytes. The main blood condition then in this disease or syndrome, when any alteration of the blood picture is noted, is one of lymphatic leukaemia though in
certain cases it has been thought that a myelogenous type of leukaemia has been responsible for the enlargement of the glands.

A further interesting group was one in which there was associated iritis or iridocyclitis. A number also were reported (seven) in which attention was drawn to associated endocrine disturbance whilst one was attributed to gout. No cases were available due to plumbism or iodism, and no pathological data were available to indicate the morbid histology to be found in these latter cases.

We get, therefore, what some term symmetrical lymphomata, diffuse or focal lymphocytic infiltrations which, it has been suggested, are due to chronic inflammatory processes and cases due to lymphocytic infiltration in association with a pathological blood picture.

With regard to the cases of sarcoma, some writers have described, and even Mikulicz, has suggested that there may be a gradual evolution in the condition under consideration, from simple lymphoma through leukaemia to sarcoma. Others have denied the likelihood of such an evolutionary process
and maintain that the symptom complex can be present in them all without there having been any transition from the simple to the malignant forms. Yet it has been shown that sarcomata in many cases show such marked histological resemblance to inflammatory processes that some workers are inclined in a certain sense to accept the theory of inflammatory origin of these tumours, especially with regard to the lymphosarcomata.

With regard to the morbid histology and the blood pictures found in the writer's own series of cases, these will be found in detail in the histories of the individual cases in a later section, but it suffices to say that these cases merely bear out the observations noted in the cases studied in the already published literature on the subject and discussed in the foregoing paragraphs.
SIGN S, SYMPTOMS
AND DIAGNOSIS.

In the foregoing pages, we have discussed the recognition of the condition and the accumulation of the literature on the subject, and also have extracted from the literature information as to the types of pathological changes met with in the various cases. In the present section the object is to discuss the diagnosis and the differentiation of the various types of the syndrome, and to describe the clinical picture with which one meets.

The term "diagnosis" means more than merely naming a disease; it demands an intelligent recognition and knowledge of the various aetiological factors, the nature and sequence of the pathological change and the recognition of the influence of the patient's surroundings, and even occupation and past medical history of the individual; furthermore, an accurate diagnosis is a primary consideration in arriving at a correct prognosis and effective treatment of any medical condition whatsoever. Whilst a description
has necessarily to give a "typical" picture, bringing in all the usual signs and symptoms that may be encountered in a large group of such disease, yet as in all clinical pictures there are variations from type in the individual cases as met with at the bedside or in the consulting room. The ailment as met with in individuals, may only in a small part fulfil these apparent requirements. Many of these cases have been already referred to in the condition under discussion, as atypical forms or "formes frustes."

In arriving at a diagnosis, one relies upon the symptoms and signs of the disease. In talking of symptoms, one divides these up into those evidences of the disease which are observed by the patient himself - these are often referred to as "subjective symptoms" and a further group termed "objective" are those evidences recognised by the physician on examination. In this group, we could include the physical signs and also laboratory tests.

With these few facts in mind, let us consider the appearance of a typical case. The patient presents rather a peculiarly stupid face, which although easy to recognise, is difficult to describe concisely. The swelling of the parotid glands fills up the hollows in front of and below the ears, and although not as a rule so pronounced as
one gets in epidemic parotitis, it is quite definite and broadens out the lower part of the face, giving rather a "heavy" appearance to the person. The submaxillary glands when enlarged, also show themselves in the rounding off of the chin. The eyes are nearly closed and the patient has the aspect of peering; this closing of the eyes is due to the enlargement of the palpebral portion of the Lachrymal glands, and gives the patient a somewhat sleepy appearance. There may also be a swelling and bagginess in the region of the lower lid due to the swelling in the region of the lower conjunctival fornix, caused by the enlargement in the Lachrymal glands of Krause. In a well marked case, with glands in the floor of the mouth and below the tip of the tongue enlarged, the mouth may be slightly open and the tongue appear too big for the mouth; this tends to make the patient have a stupid appearance.

The patient's main complain is usually the disfigurement caused by the condition, and there may be no other complaint. There is also some discomfort referred to in the eyes, and a tendency to sleepiness. The discomfort of the eyes is due to some conjunctival irritation, and also there may be a complaint of difficulty in reading.
A rather interesting point is noted in this connection in the author's "Case One."

The function of the glands is usually not markedly interfered with, though in certain cases lachrimation (13) has been noted, in others salivation (1, 72) and in yet others (16, 73, 74, 75, 76 & 77) xerostomia has been a fact commented upon. There are also symptoms referrable to the interference with function, due to the actual size of the enlarged glands and many cases are on record where there has been dysarthria, (1 & 75), and in others dysphagia. (1, 72 & 75). Both of these conditions are definitely traceable to the enlarged glands interfering firstly with articulation and secondly with deglutition, as has already been mentioned in the description. It was also noted that in one case of the series, deafness was due to the enlargement of the glands in the mouth and pharynx. (78)

The usual sequence of onset shows that the lachrymal glands first enlarge, (1, 16, 79, 80, 81, 82) to be followed at a later date by the enlargement of the salivary glands the parotids being those most usually affected. We have already mentioned the occurrence of cases of enlargement of the lachrymal glands alone, or the salivary glands alone, and these have been classed as
the "formes frustes" of Mikulicz Disease. Swelling in the region of the orbit, whether of definite tumour formation or merely infiltrations of lymphoid tissue, do not enter into the classification of Mikulicz Disease or syndrome. This term has been reserved for those cases of swelling of the lachrymal and salivary glands, and not merely swellings in the neighbourhood of these structures.

There may be spontaneous resolution without any treatment and one or two cases have been noted in which spontaneous resolution has coincided with some febrile condition, and in one case resolution has occurred under such conditions, with recurrence of the swelling after a subsidence of the febrile state. Besides the simple enlargement of these glands, we get enlargement in leukaemia and lymphademona. Sarcoma may also affect these glands.

As regard the age groups in which one may be likely to find the condition, the following graphs prove rather interesting: those simple cases of lachrymal and salivary gland enlargement with no change in the blood picture and no enlargement of groups of lymph glands, we might term "pure Mikulicz." These are shown in the figure represented
by the continuous black line, and between the ages of 11 to 60 appears to be the most likely period of occurrence, with a rather higher peak incidence in the decade 41-50. Those cases with associated enlargement of the lymph glands but showing no blood change, are represented with the continuous red line, and show the highest incidence in the age group 11-20, with a rapid falling off to the age of 40 and from then onwards almost an equal incidence.

The dotted red line shows the cases associated with lymph gland enlargement, and a pathological blood picture - these blood changes were in the nature of lymphatic leukaemia as we have already noted in the pathological discussion: the highest incidence here appears to be in the first decade of life, whereas the graph drops suddenly in the second decade and shows two peaks of almost equal incidence at the third, and again at the sixth decade.

With regard to sex incidence, it is interesting to note that the occurrence amongst the males is definitely greater. About 50% more male cases are recorded in those of "pure" Mikulicz, whilst the distribution in those cases with blood changes and associated lymph gland enlargement, the male incidence is preponderant though
-23-

![Graph showing the percentage of lymph gland changes over different age groups.]

<table>
<thead>
<tr>
<th>DECADE</th>
<th>0-10</th>
<th>11-20</th>
<th>21-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>61-70</th>
<th>71-80</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Lymph Gland No Blood Change</td>
<td>1.83%</td>
<td>17.43%</td>
<td>19.34%</td>
<td>15.87%</td>
<td>9.01%</td>
<td>9.17%</td>
<td>7.33%</td>
<td>1.83%</td>
</tr>
<tr>
<td>With Lymph Gland No Blood Change</td>
<td>3.96%</td>
<td>30.99%</td>
<td>23.67%</td>
<td>7.69%</td>
<td>11.83%</td>
<td>11.53%</td>
<td>11.53%</td>
<td></td>
</tr>
<tr>
<td>With Lymph Gland With Blood Change</td>
<td>3.28%</td>
<td>3.57%</td>
<td>17.86%</td>
<td>7.14%</td>
<td>7.14%</td>
<td>17.86%</td>
<td>7.14%</td>
<td></td>
</tr>
</tbody>
</table>
not to a very great extent. Those cases with lymph gland enlargement but no blood change, show the most marked incidence amongst the males:

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Lymph Gland - No Blood Change</td>
<td>62</td>
<td>47</td>
</tr>
<tr>
<td>With Lymph Gland - No Blood Change</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>With Lymph Gland - With Blood Change</td>
<td>15</td>
<td>13</td>
</tr>
</tbody>
</table>

An interesting comparison with these cases, is the age and sex incidences in cases of chronic lymphatic leukaemia. It has been stated that this disease develops most frequently late in life, as a rule in individuals between 45 and 60, and that males are affected twice as frequently as females. The findings as shown by the graph in the series of cases of a blood change do not fully carry out this rule as stated, yet those cases which have been called "pure" Mikulicz seem to fall in with this rule of age and sex incidence, whilst the group of cases described as occurring with lymph gland enlargement and no definite blood change appears to follow the rule of age and sex incidence of lymphogranulomatosis, pseudoleukaemia or Hodgkins disease, in which it has been stated that it occurs most frequently in the second and third decades and men are more frequently affected than women.

Those cases which are included in this paper under the
heading "with blood change" are those cases with definite increase of white cell count, and also those cases which though not showing relative increase of white cells, show a definite preponderance of lymphocytes in the blood picture.

With regard to the prognosis in these cases, the first group, that is those cases with no blood change and no lymph gland involvement, this is definitely good as to life; many recover, another large percentage improve, whilst a certain number show no change over a period of observation. In those cases with lymph gland involvement but no change in the blood picture, the prognosis is not so good. A high percentage of these are reported to have died and a larger percentage show no change, and those reported as improved are also in a small percentage. The group with lymph gland involvement and a definite leukaemic blood picture is the worst as regards prognosis and shows the highest percentage of cases reported as died, a very small percentage reported as recovered, whilst the number reported as with "no change" and "improved" are about level.
<table>
<thead>
<tr>
<th>No Lymph Gland</th>
<th>Recvd.</th>
<th>Imp.</th>
<th>No Change</th>
<th>Died.</th>
<th>No Note as to Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Blood Change</td>
<td>18.18%</td>
<td>20.0%</td>
<td>9.09%</td>
<td>3.63%</td>
<td>49.09%</td>
</tr>
<tr>
<td>With Lymph Gland</td>
<td>23.07%</td>
<td>7.69%</td>
<td>15.38%</td>
<td>13.23%</td>
<td>34.61%</td>
</tr>
<tr>
<td>No Blood Change</td>
<td>7.14%</td>
<td>21.42%</td>
<td>14.28%</td>
<td>39.28%</td>
<td>17.85%</td>
</tr>
<tr>
<td>With Lymph Gland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With Blood Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TREATMENT.

The next aspect of the subject for discussion is the treatment of the condition.

In treatment one ought to aim first at the removal of the cause - if this is not possible we may succeed in neutralizing the effect or influence. One of these methods may suffice to cure all symptoms and troubles of the patient but in many cases we have also to deal directly with symptoms, and in doing so have recourse to remedies that have no influence on the underlying disease, though in doing this we must not forget that symptoms are only of secondary importance to the disease causing them. Finally our duty is to counteract the tendency to death, which may be the natural course, or may be accidental from some complications occurring during the disease.

Until an exact knowledge of the aetiology gives us a clear understanding of the primary causal factor of the condition, no scientific therapeutic technique can be built up. Any attempt at treatment has to be empirical where by trial and error a reliable method of dealing with the condition is arrived at. A certain amount of help is afforded if a condition newly observed shows some resemblance to the pathological picture of an already known
disease. In such a case it is quite feasible to believe and to act upon the assumption that what has been proved to be of value in the already known disease, will most likely prove of value in the new condition.

With regard to Mikulicz Disease, although many theories as to its exact aetiology have been put forward, no definite decision has been arrived at to explain its occurrence. Some writers suggest that it is probably due to some infective processes (1, 11 and 85) and the methods of treatment in certain cases, with which we will deal later, seem to give weight to this theory; in others it is suggested that it is some blood disease, and certainly the fact that one sees a similar symptom complex arising in types of leukaemia seems to give this theory a certain amount of standing.

The earlier workers began treating the condition in what we might term an empirical method, and in fact we might almost say that this method is still the one which is used, as no definite specific therapeutic technique has been evolved. Drug treatment has held the foremost place from the first. The main drugs which have been used have been, first, Potassium Iodide, which when we compare the results obtained, seems to be the most successful amongst the medicaments used. Arsenic, mercury and combinations
of these drugs have also been tried, but Potassium Iodide alone seems to have been the most successful type of treatment.

Later workers (77 and 86) have begun using the radiation given off by Radium and also X-rays. This method seems to have superceded to a large extent the other methods of treatment, especially in those cases where there has been some associated lymph gland enlargement, or lymph gland enlargement with a leukaemic blood picture.

Many cases have shown that operative removal has not resulted in recurrence, but operative removal appears to be only indicated for either cosmetic reasons or cases showing definite pressure symptoms, even this probably would be better delayed until other methods of treatment had been attempted.

With regard to the theory of an infective causation of the condition, it is interesting to note that in certain cases removal of septic tonsils, (87,88) extraction of teeth, (89) and in other cases the administration of Vaccine (67, 90 and 91) have resulted in recovery or definite improvement in the condition, and in other cases treatment with endocrine glands (63, 66) have shown marked improvement.
Below are appended figures showing a comparison of the different methods of treatment adopted most generally. A glance at these figures will bear out what has been said as to the efficacy of the various types of treatment that have been described in the series of cases extracted.

**NO LYMPH GLAND - NO BLOOD CHANGE.**

<table>
<thead>
<tr>
<th></th>
<th>X-RAY</th>
<th>RADIUM</th>
<th>RAD</th>
<th>ARSENIC</th>
<th>POT.IODIDE</th>
<th>MERCURY</th>
<th>ARSENIC</th>
<th>POT.IODIDE</th>
<th>MERCURY</th>
<th>ARSENIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
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**WITH LYMPH GLAND - NO BLOOD CHANGE.**

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NO LYMPH GLAND - WITH BLOOD CHANGE.

WITH LYMPH GLAND - WITH BLOOD CHANGE.

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The numbers in the columns refer to actual cases.
NOTES OF CASES.

The following are five cases set out in detail to illustrate the types of the condition which may be met, one of these, case 4, has already been published.

Case 1 occurred in the writer's own private practice and was observed throughout.

Case 2 was one which had been mentioned to him by a Consulting Physician in Newcastle upon Tyne, and whom he had the opportunity of examining.

Case 3 was a case which had been treated in the Royal Victoria Infirmary, Newcastle upon Tyne, and the notes and photographs of which have been very kindly supplied by Professor Beattie.

Case 4 - a case occurring in Carlisle and the notes of which have been published by Dr. J.A. Ross, whose permission has very kindly been given to use the notes and photographs.

Case 5 is one which temporarily came under the writer's care, and then passed out of his hands on the return of the patient's own medical attendant from holiday.

........................................
NAME: Mr. C. Horsley.          AGE: 70 years.

OCCUPATION: Secretary of an Insurance Company (Retired)

HISTORY: The patient has for some thirty years suffered from indigestion, and in
February 1930 had a definite haematesis. After recovery from this he continued with symptoms suggesting Pyloric Stenosis, and in the following year he was operated upon, a gastro enterostomy being performed by Mr. Hamilton Barclay, Newcastle. This considerably relieved his condition and he had very little trouble from the indigestion since that time. Apart from this he had a fairly clear history although he had always been of the nervous, highly strung type.

In 1916 he collapsed through over-work and this was put down to "nervous strain."

In 1924 he suffered from phlebitis in the left leg and at that time there was a slight pulmonary involvement suggestive of pulmonary embolism.

In 1933 early in the year he had an influenzal bronchitis with a swinging temperature for a week or two. He brought up a lot of muco-purulent sputum but this gradually improved. No tubercle bacilli were found in this.

In May 1933 he had a slight attack of diarrhoea with some mucus in the motions which was thought attributable to eating strawberries. From the time of his attack of
influenzal bronchitis in March he never really felt well, although by May he was certainly improved. During June 1933 he noticed a reddish growth appear over the medial aspect of the left eye and to a slighter extent on the right eye. He consulted Mr. Arkle, an Ophthalmic Surgeon, during my absence on holiday. Mr. Arkle found at that time that the plica semilunaris was thickening and growing outwards over the surface of the sclera and on evert ing the lower lid some small swellings, like granulations, were noted in the lower conjunctival sacs.

At this time there was no discomfort, the only complaint being the unsightliness of the condition - the lachrymal glands were not very noticeable at this time. In July 1933 he began to complain of discomfort in the eyes which gradually increased and was found to be due to a slight entropion of the lower lid, causing the eyelashes to irritate the surface of the cornea. This entropion was caused by the increase in size of the swellings in the lower fornix of the conjunctiva, which had assumed the size of half a date stone in length, and when the lower eyelid was everted, there was some difficulty in returning it to its normal position, the patient himself discovering that by drawing the loose skin, below and lateral to the lower eyelid, in a downward and outward direction he was
able to return the growth and eyelid to their normal relations.

On examining the eye it was also noted that the palpebral fissures were narrowed and swellings were noticeable over the upper eyelid towards the lateral canthus, also the lower eyelid was puffed out, due to the swelling already described in the lower fornix.

On drawing the upper eyelids upwards and laterally it was noticed that the lachrymal gland was considerably enlarged, and growing forwards and downwards over the eyeball in both eyes. The appearance of both the enlarged lachrymal gland and the tumour in the lower fornix was rather paler than the normal conjunctival mucous membrane and showed small blood vessels running over its surface. At this time he also complained of sweats occurring on exertion and also during the night. He was very fatigued and sleepy.

About this time he was seen in conjunction with Dr. Spence who suggested that his condition appeared to be one of septic absorption, the focus of the sepsis not being very apparent, but possibly from low grade bronchitis, as no other explanation could be found for the sweats, fatigue and sleepiness.

On 22nd August, 1933, an upper pre-molar, which had shown
slight sepsis was extracted. Following this a rather remarkable increase in the size of the tumours took place, they also assumed a plum coloured appearance which persisted for about a week to ten days.

By September 1933 the lachrymal glands were more definitely enlarged and very easily demonstrable whilst the plica semilunaris had further encroached on to the eyeball, and was nearly as far forward as the edge of the cornea. On 16th October, 1933 another tooth which was slightly septic was removed, and again this resulted in a temporary increase in the size of the tumour and a return of the plum colour which had previously been noticed in August. The discomfort in the patient's eyes had increased and he was now finding it very difficult to read for more than a very short time indeed, so that it was decided that Mr. Arkle should remove the tumours in the lower conjunctival sac, and this was done on the 27th October, 1933. The tumours were sent for pathological examination and a rather alarming report was received from the pathologist:

"The first impression conveyed by examination of this tissue is that of a round-celled sarcomatous condition, but it may be a lymphoid granuloma. I do not think at this stage that from the histology Mikulicz's disease can be definitely diagnosed or excluded. Is the condition symmetrical and is there any change in the blood? In the first instance a film might be examined. The specimen is being further studied, and we shall be extremely obliged for a note on the clinical progress."
Case 1

Showing diffuse infiltration with round cells.

Fig. 1b.
CASE 1

Fig. 2.

ENLARGEMENT FROM SMALL PHOTOGRAPH TAKEN ON OPERATING TABLE.

EYELIDS SHOWN EVERTED.
As this was so disturbing it was thought a corroboration of this would be desirable, and a second report was obtained from another source:

"The section shows conjunctiva and sub-conjunctival tissue, infiltrated with a lympho-sarcoma or leukaemic deposit in accordance with the leucocyte count. (Mikulicz's disease is a clinical and not a pathological entity)."

Photographs of the microscopic sections were made, (Figs. 1a and 1b.) At the time of the operation it was thought that a pictorial record might be interesting and an attempt was made to take a picture of the condition of the eyes on the operating table; as however the camera was only a small one, the resultant picture is perhaps not quite as clear as it might be, but sufficient can be seen to indicate the position of the tumours (Fig. 2).

There was still at this time general depression, lassitude and a desire to sleep. The wounds in the conjunctiva healed perfectly and there was no recurrence. The plica semilunaris continued to encroach over the surface of the eyeballs on both sides, and the lachrymal glands were gradually becoming more disfiguring, and by the beginning of November 1933 could be easily seen bulging the outer parts of the upper eyelids, and without drawing up the eyelids they could be noticed spreading forwards and pushing the eyeballs slightly forwards. The disfigurement so caused was giving a great deal of distress to the patient who was
highly sensitive. Just in front of the ears and in the space below the lobules of the ears, there appeared a gradual filling up of the hollows. This came about rather slowly and it was some time before it was realised that the parotid glands were slightly enlarged, but this became more apparent. The parotid glands could be felt filling up the space below the lobules and in front of the tragus, and appeared to be rather fibrous in structure. An attempt was made to photograph the patient to show this stage. (Fig. 3)

There was one small enlarged gland under the symphysis menti, but the other salivary glands could not be said to be enlarged. There was no salivation nor dryness of the mouth. A blood picture showed a slight anaemia and a slight increased white count.

Red Cells \[\ldots\] 4,200,000 per Cub.mm.
Haemoglobin \[\ldots\] 80%.
White Count \[\ldots\] 9,000 per Cub.mm.

RED CELLS show some hypochromia but are regular in size and shape. No nucleated red cells seen.

LEUCOCYTES. Judging by the film there is a slight leucocytosis.

Differential Count.

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<td>Basophils</td>
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CASE 1

Fig. 3a.

SHOWING FULLNESS IN FRONT OF AND BELOW THE EARS, AND FULLNESS IN THE REGION OF THE UPPER EYELIDS TOWARDS ITS OUTER PART.
CASE 1

![Image](Fig. 4a)

Showing that the hollows in front of and below the ears have returned and that the eyelids have not the same puffy appearance. In Fig. 4b, the Plica Semilunaris can still be made out, but it had by this time shrunk and later still became quite normal in appearance.

![Image](Fig. 4b)
This blood picture shows a slight neutrophilic leucocytosis without left shift, associated with a moderate degree of normocytic (secondary) anaemia.

On 16th November, 1933, it was decided on account of the swelling and disfigurement being so marked to give Deep X-ray Therapy and this was done by Dr. Ramage, who states that the rays were generated at 185 kilovolts and 4 milliamperes, and were filtered through 0.5 mm Zinc and 2 mm Aluminium. The focus-skin distance was 35 cms and the area of the field about 175 sq. cms. Each side of the face received $\frac{1}{4}$ unit skin dose on the following dates, 16th and 17th November, 1933.

After the X-ray Therapy there was a complaint for a day or two that the saliva was sticky. The patient was also given at this time a few exposures to Ultra Violet Rays at his own request. His general appearance and colour showed improvement and though for the first few days there was little reduction in the lachrymal gland, by 21st November 1933, there was marked reduction in the size of the lachrymal gland and the thickening in the region of both the parotids had disappeared, the palpebral fissures were widened, the plica semilunaris had shrunk, the colour was less angry and the eyes appeared to be less puffy. The hollows in front of, and below the ears had returned and the patient looked more alert. He was then photographed. (Figs. 4a and 4b).
On 29th November, 1933, the patient complained of some abdominal discomfort and there was slight mucus in the motions. The sweats from which he complained were not now so severe as earlier in the year. There was still a certain amount of lack of appetite and mild constipation.

On 31st December, 1933, a blood picture was taken and showed a similar result to the previous one.


Differential Count.

| Polymorphs | : : : : | 82.0% |
| Lymphocytes | : : : : : | 12.5% |
| Eosinophils | : : : : | 0.5% |
| Hyalines | : : : : : | 5.0% |

Report.

There is an apparent polymorph leucocytosis. Red cells show very slight anisocytosis and rarely some slight polychromasia, but no other changes are found. Mean diameter of red cell 7.1 (Normal).

On account of the continued lassitude and complaints of abdominal discomfort, an X-ray screen was carried out by Dr. Drummond after a Barium meal. A report of the screening showed there was nothing abnormal in the gastro-intestinal tract. Whilst in the Nursing Home for observation and X-ray examination the patient's appetite and general condition improved, and no recurrence of the enlargement of
Diagramatic drawing of the condition. This was made after the removal of the datestone-like growth in the lower fornix but this has been put in the drawing. The appearance although somewhat diagramatic is fairly true to life.
the parotid or lachrymal glands has been noted since.

A rather interesting report was sent by Mr. Arkle who saw the patient again on the 11th April, 1934 with regard to his eyes. He states:-

"I am delighted with the appearance of his eyes. The lower lids seem to have gone back into perfect apposition, without any entropion or ectropion. His refraction is rather interesting. When I first saw him his distance vision had obviously gone off a good deal, as he found he could no longer see so well at golf. I found he was seeing badly with his then glasses, but that after correcting a good deal of astigmatism, against the rule, (i.e. hypermetropic astigmatism, axis horizontal), he again came up to 6/6. Now he finds that these glasses are useless and on testing I find the astigmatism is practically all gone. I have no doubt at all that these nodules in the upper and lower lids were squeezing the eye and causing a little bulging of the cornea in the horizontal axis, this giving rise to the astigmatism. This has now subsided and he again sees with a very slight correction. Media and fundi appear normal. As before, his left eye is amblyopic but that I am afraid will always be so."

About two weeks after the excision of the tumours in the lower conjunctival fornix a water colour drawing was made of the condition, and an attempt was made to portray the date stone like growth as well as the thickened and enlarged plica and the swollen lachrymal glands. (Fig. 5).
SECOND CASE.

NAME: Mrs. Margaret Curry,  AGE: 36 years.
West Kyloe,
Beal, Northumberland.

PRESENT ADDRESS: 10, Palace Street, Berwick on Tweed.

Admitted to the Royal Victoria Infirmary,
July 8th, 1927 - under Dr. Hume.

Complained of swelling in the glands of the neck and face.

HISTORY.

In February 1927 she complained of feeling sick and listless, and if she stopped working she had difficulty in keeping awake. She noticed she was puffy about the eyes.

March 1927, she had an attack of Erythema Nodosum in both legs.

In May 1927 she noticed a small lump in her left cheek, and swellings in front of her ears and around her eyes, and at this time she noticed her eyes had begun to grow misty. At first she was thought to be suffering from mumps as there had been a few cases in the neighbourhood.

July 1927 she had a further attack of Erythema Nodosum on the arms and she also noticed that the puffiness round her eyes had become more pronounced, until actual lumps seemed to be appearing on the outer side of the upper eyelid - the left side swelling appearing before the right. The regions of the Parotids were very much swollen and stony hard, and they were very painful at night. The jaws were stiff and
she had difficulty in opening them and had no appetite for food. During this month she was admitted to the Royal Victoria Infirmary, where after about two weeks the glands began to subside. The saliva began to flow freely before the glands cleared up. This salivation is at times still troublesome (November 1933) and she says she still has some stiffness in the jaws on occasions.

**FAMILY HISTORY:** Nil of note. Father and mother healthy. Eight brothers and sisters all healthy.

On admission to the Royal Victoria Infirmary it was noticed that there was a swelling of a hard nature in the region of the parotid gland, but there was no tenderness and no fluctuation. There was a hard knot in the left cheek which suggested enlargement of the parotid duct. The right parotid gland and duct were similarly swollen, the swelling on this side was hard but no tenderness or fluctuation was noticed. There was a small swelling in the region of the left submaxillary gland and a slight swelling at the lateral angle of the upper eyelid of both eyes. The patient had a large amount of saliva in the mouth and the eyes tended to lachrymation. The patient had difficulty in opening her mouth wide.

The teeth were broken and septic. The tongue clean - appetite very poor and she vomited if much food was given. Constipated. Wasserman - negative.
No notes on the blood picture are available.
She was discharged after two weeks with the swellings very much improved.

In November 1927, she was again admitted to the Royal Victoria Infirmary, under Mr. J.S. Arkle, who writes:-

"She then had all the symptoms of a severe Irido-Cyclitis in both eyes, with K.P. and posterior synechiae. In the right eye the pupil was occluded and iris bombe present. We next saw her in February 1928, when we found the acute attack had subsided, but that she had iris bombe in both eyes. She was later admitted and had an iridectomy done on each eye. Since then the condition appears to have settled down gradually, except in 1931 she appears to have got a slight flare up as we note that K.P. is present again. The swelling (parotid and lachrymal) had quite subsided by the time we saw her in November 1927."

19th November 1933, the patient was re-examined on this date at her own home and at this time appeared to be very fit and is quite capable of all her own work. There is no sign of any swelling of either the salivary or lachrymal glands. She has marks on her left leg of fading Erythema Nodosum which she had a few weeks ago. No lymph glands to be noticed. She has signs in both eyes of an iridectomy having been performed.

22nd March 1934, there was no sign of any swelling of the lachrymal or salivary glands, and Mr. Arkle writes:-

"She still has the remains of her Irido-Cyclitis. In the right eye the iris has evidently been adherent all over so that the iridectomy has not relieved the condition, Iris bombe is still present. In the left eye the pupil is blocked but the iridectomy has restored communication between the anterior and posterior chambers and she has 6/12 vision. She still has spots of recent looking K.P. on the back of her cornea, which suggests that whatever the toxic causes was originally it is not yet cured."
THIRD CASE.

NAME: Mr. Robin Bell.  
AGE: 53.

ADDRESS: 5 Shakespear Street,  
North Shields.

Admitted to the Royal Victoria Infirmary,  
22nd April, 1926 - under Dr. Beattie.

Complained of enlarged glands in the neck - both sides.

HISTORY.

March 1925, there was noticed some enlargement of the glands in his neck, this very slowly increased until March 1926, when his doctor, Dr. H. Adams of North Shields, excised one of the enlarged glands and as a result of the examination of it, arranged for him to be admitted to the Royal Victoria Infirmary, where he was found to be suffering from enlarged glands in the submaxillary space on both sides of the neck, particularly towards the angle of the mandible. The glands were discrete.

The patient was a good colour, the conjunctiva were normal, the pulse 92, strong and regular. The arteries were not thickened. The finger nails showed a slight degree of clubbing. No visible apex beat. The apex was in the fifth intercostal space, slightly displaced outwards. The heart sounds were normal but difficult to hear.

Fig. 6.

Showing patient before X-ray treatment — swelling round about the eyes, in front of and below the ears.
CASE 3.

Fig. 7.

SIDE VIEW SHOWING MARKED INFILTRATION BOTH ABOVE AND BELOW THE EYE. THE SWELLING IN FRONT OF EAR IS BETTER BROUGHT OUT IN THIS PICTURE.

Slight constipation.

Previous History. Nothing of note except rheumatic fever when 46 years of age.


The patient was treated by X-rays daily for one month whilst in hospital, and afterwards he attended the X-ray Department once a week for two months, following which he had three months without treatment, and then a further three months with exposures to X-rays once a week.

25th January 1927. On this date there were some glands in the axilla and groins, no glands in the right side of the neck, but three felt in the left side. The spleen was just palpable coming below the costal margin on inspiration. No blood counts or blood films were available for this period.

He was again admitted to the Royal Victoria Infirmary on the 13th May, 1927, when it was found that he had enlarged glands present in both submaxillary spaces, in the posterior triangles and supraclavicular regions, in axilla, groins and femoral triangles. There were also enlarged epitrochlear glands and the parotid glands were enlarged on both sides. There was also some swelling in both orbits. There were nodules in the skin on the chest and flanks. The patient
had a fairly good colour and appeared in good condition.

Alimentary System. Teeth in poor condition - some old septic stumps only present.

Urinary System. Slight difficulty on micturition with a griping pain in the perineum and occasional nocturnal frequency and some dribbling of urine. Specific gravity of urine 1.025. Reaction acid. No abnormal constituents or deposits.

Nervous System. Cranial nerves normal. Pupils respond to light and accommodation. No knee or ankle clonus. Plantar response strongly flexor both sides. The eyes show proptosis which was first noticed February 1927.

There is a crop of Herpes Zoster on the right side of the neck which extends along the branches of the second cervical nerve.

20th May 1927. Blood film. Red cells show slight anisocytosis and poikilocytosis but no abnormal or nucleated forms present. Polymorphs predominate (roughly 60%). Lymphocytes large and small present. No suggestion of lymphatic leukaemia.

23rd May 1927. Glands removed from over pectoral region, and sent for Pathological examination.

25th May 1927. Seen by Mr. Wardale with regard to enlargement of lachrymal glands.

30th May 1927. Herpes on neck clearing up.
CASE 3.

Fig. 8.

Showing the enlargement of the lachrymal gland growth downwards and forwards over the eyeball.
Case 3.

Fig. 9.

Showing skin nodules.
31st May 1927. Some nodules have now appeared on the patient's back - irregular in distribution and showing signs of slight inflammatory change on the surface.

7th June 1927. Bleeding from the rectum. On examination haemorrhoids noted, also some small nodules the size of a pea felt. ? lymphatic nodules or fibrosed haemorrhoids.

14th June 1927. Swelling of feet and legs on getting up.

Pathological Report on Gland.

The appearances here are on the whole more suggestive of a sarcomatous condition than lymphadenoma. The structure of the gland is entirely altered and there is diffuse infiltration with small round cells, such as one sees in lympho-sarcomatous growth. Some of the cells are, however, not perfectly round but are of short oval type. There is a well marked fibrosis and there is apparently also some infiltration beyond the normal confines of the gland. There is more fibrosis in the gland than one expects in a rapidly growing sarcoma. In this way the appearances are rather suggestive of lymphadenoma. There is some hyaline change in the arterioles and there is a considerable degree of vascularity. There are a few large mononuclear endothelial cells but there are none of the typical lymphadenoma giant cells. There is nothing in the least degree of tuberculosis in this specimen.
CASE 3.

Fig. 10.

SHOWING PATIENT AFTER X-RAY TREATMENT. FULLNESS BELOW THE EYES AND IN FRONT OF AND BELOW THE EARS HAS ENTIRELY DISAPPEARED.
CASE 3.

Fig. 11.

SHOWING THE PATIENT AFTER X-RAY TREATMENT. FULLNESS BELOW THE EYES AND IN FRONT OF AND BELOW THE EARS HAS ENTIRELY DISAPPEARED.
Pathological Report on Skin Nodule.

"Had one known nothing of the previous history of this case, I think one would have regarded it as a small round cell sarcoma, infiltrating the sub-cutaneous connective tissue and fat. I do not think that it could be diagnosed on ordinary histological grounds as a lymphadenoma. I am returning herewith also the section sent by Dr. Adams, from the Clinical Research Association. The appearances are those of a diffuse fibrotic condition affecting subcutaneous tissue and fat. There is a very little cellular infiltration here, the structure for the most part being fibrous. There is no trace of glandular tissue here and from the appearance presented I do not think a definite diagnosis of lymphadenoma is possible."

5th August 1927. The patient had a course of X-ray treatment to the axillae and groins for skin nodules. The skin nodules have now practically disappeared, the glands decreased and the swelling over the eyes very greatly decreased. The patient is continuing X-ray treatment for two weeks as an Out-patient. Photographs showing the patient's condition before the X-ray treatment and after it, follow.

Since the above report the patient has died, but it has been impossible to find out the date, although there was definite recurrence of glandular enlargement before death.
FOURTH CASE.

NAME: Mrs. B. AGE: 37 years.
First seen January 8th, 1921. (J.A. Ross).


FAMILY HISTORY: Excellent. Father and mother alive and healthy, 71 and 61 respectively. Three sisters and one brother alive and well - none dead.

HISTORY: The patient complains of difficulty in keeping eyes open - eyelids feel so heavy. Also a frontal headache. She looks as if she were half asleep and struggling to keep awake. The palpebral fissures are narrowed, the upper lids drooping and bulging above, eyebrows strongly arched and elevated by forcible contraction of occipito-frontales. Her forehead is horizontally wrinkled by the effort. She says her eyes have always been prominent, but there appears to be some proptosis. Palpation shows bulging below the eyebrow to be due to the hard finely nodular, enlarged lachrymal gland. The enlarged palpebral portion is easily seen on everting the lid.

Parotid Glands. It is difficult to feel certain that they are enlarged.

Submaxillaries and sublinguals normal.

\[
\begin{align*}
V.R. &= 6/12 \quad \text{with} \quad +0.75 \; \text{cyl} \; 90^\circ = 6/6 \\
V.P. &= 6/12 \quad \text{with} \quad +0.75 \; \text{cyl} \; 90^\circ = 6/6 \quad \rightarrow \quad 6/5.
\end{align*}
\]
CASE 4.

Showing marked broadening of the face due to swelling of the parotids and also fullness round the eyes, especially in the region of the upper eyelid towards the outer aspect.
Fundus, fields, tension, muscles, pupil reaction - no abnormality.

A provisional diagnosis of Mikulicz Disease was made and she was put on arsenic.

PROGRESS.


12th April 1921. Sublinguals, parotid still bigger, submaxillary slightly enlarged, lachrymal unchanged.

July 1921. Palpebral portion of lachrymal glands (both) excised.

Shepheard Walwyn.

13th April 1921. Swelling of eyes and cheeks fluctuate in size; less marked at night. Parotids swell, especially during eating - very painful during later part of the day. Shortness of breath and palpitation for three months past. Losing weight and appetite. Feels weak, anxious and nervous, sweats through the night, noticed her colour became paler. During last four weeks has been conscious of swelling of neck. Parotid much enlarged - firm and smooth - no tenderness. Lachrymal glands firm and the size of half a filbert nut. Ptosis of temporal half of lids.
Submaxillary and sublinguals much enlarged. Thyroid right lobe was definitely enlarged and firm. There was no enlargement of tonsils, lymphatic glands, liver or spleen. Gums, buccal mucosa, tongue and palate found healthy. Urine - no abnormal constituents.

**Blood.**

- **Erythrocytes**: \(3,750,000\)
- **Haemoglobin**: \(70\%\)
- **Leucocytes**: \(7,600\)
- **Index**: \(0.9\)
  
  Variation in size and staining of R.E.C.

**Differential Count.**

- **Polymorphs**: \(64\%\)
- **Lymphocytes, large and small**: \(29\%\)
- **Eosinophils**: \(7\%\)

Wasserman - Negative.

Arsenic given in increasing doses.

8th May 1921. Felt much stronger. Lachrymal gland only showed diminution. X-ray treatment begun. Loss of weight - \(3\frac{1}{2}\) lbs.

**Blood.**

- **Red Blood Cells**: \(3,300,000\)
- **Haemoglobin**: \(68\%\)
- **White Blood Cells**: \(8,000\)

Average size Red Blood Cells increased. Poikilocytosis, Polychromasia and basophil stippling. Differential Count similar to previous.

Photographed.

2nd July 1921. Palpebral portion lachrymal glands excised.

thyroid normal to touch.

**Blood.**

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<tbody>
<tr>
<td><strong>Red Blood Cells</strong></td>
<td>...</td>
<td>4,600,000</td>
</tr>
<tr>
<td><strong>Haemoglobin</strong></td>
<td>...</td>
<td>85%</td>
</tr>
<tr>
<td><strong>White Blood Cells</strong></td>
<td>...</td>
<td>8,000</td>
</tr>
<tr>
<td><strong>C.I.</strong></td>
<td>...</td>
<td>0.92</td>
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Poikilocytosis and Polychromasia present but not marked.

**Differential Count.**

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<tbody>
<tr>
<td><strong>Polymorphs</strong></td>
<td>...</td>
<td>66%</td>
</tr>
<tr>
<td><strong>Lymphocytes</strong></td>
<td>...</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Eosinophils</strong></td>
<td>...</td>
<td>4%</td>
</tr>
</tbody>
</table>

Lost more weight in spite of general improvement.

3rd October 1921. Improvement maintained. 4 lbs gained in weight. She remained well until the middle of November 1921, when she complained of dyspnoea, general malaise and vomiting. Urine scanty - albumin + blood - hyaline casts. She developed air hunger, cyanosis and oedema of both lungs.


**PATHOLOGICAL FINDINGS.**

Dr. Dawson (R.C.S. Edin.) Numerous follicles of a granulomatous type are present in the midst and around the gland ducts and acini. These are mostly cellular in character, and suggest tubercle follicles of an early stage.

No giant cells or necrosis was present.

No tubercle bacilli were found.

The appearances are consistent with those described in Mikulicz Disease.
CASE 4.

FIG. 51.

A = gland ducts and acini. n = small round-cells. c = cluster of cells of connective tissue type.

FIG. 52.

Lobule of lacrymal gland, showing widespread growth displacing and pressing upon the ducts and acini (A), and presenting a definitely follicular arrangement (B1, B2).
No spirochaetes were found in section stained by Levaditi's method.

Dr. Canti (St. Barts.) Section showed the structure of the gland divided into lobules. The tubules appear normal, but are pressed apart by masses of round cells containing a few fibroblasts and fibrous tissue cells. In addition to this, each lobule contains half a dozen or more islets, composed of fibrous tissue cells or fibroblasts, but containing also a few round cells. At first sight these islets appear to be separate units but a more careful study shows them to be more or less continuous with the intertubular masses already described. The capsule and connective tissue between the lobules appear normal, except for here and there a few aggregations of round cells.

Dr. Richard Connell's X-ray Notes. Treatment from 12th May 1921 to 1st November 1921 with intervals of rest. 20 treatments.

Dose one pastille, but measured at the tube side of the filter, which was 3mm. thick of aluminium and felt protection for the skin.

Frequency. Dose was given weekly to both parotids until June 23rd, when first interval of two weeks was begun. Improvement noticed from the first.

July 7th. Left parotid apparently normal, but the right
side still showed enlargement at the periphery although the whole gland was much smaller. After this date, parotid treated alternately after a fortnight's rest to the left gland. Has no malaise and weakness the day following treatment.

The submaxillary glands were not enlarged, but the sublinguals were definitely enlarged. His eyes showed some puffiness in the region of the lacrimal glands, but on elevating the upper lid the puffiness was not noted to be due to any great enlargement of the lacrimal gland. The palpebral portion of each lacrimal gland could be made out growing downwards but this was not very markedly enlarged. The conjunctiva was quite normal. The glis
FIFTH CASE.

NAME: Mr. L. Rosenvinge  
AGE: 51 years.

ADDRESS: 1, Kingsland,  
Newcastle upon Tyne.

18th July 1934. In the absence of a colleague I was called to see this patient who was suffering from an influenzal attack. Owing to the fact that I was possibly interested in cases of the enlargement of the parotid gland, it struck me that his face was very much broader than normal and his whole appearance suggested a case of Mikulicz's Disease. On examining him I found that the broadening of the face was definitely due to enlarged parotid glands on both sides. These glands were firm and smooth on palpation. They were not tender and they could be felt as definite structures which could be easily delineated on careful palpation.

The submaxillary glands were not enlarged, but the sublinguals were definitely enlarged. His eyes showed some puffiness in the region of the lachrymal glands, but on evertting the upper lids the puffiness was not noted to be due to any great enlargement of the lachrymal gland. The palpebral portion of each lachrymal gland could be made out growing downwards but this was not very markedly enlarged. The conjunctiva was quite normal. The plica
was not enlarged nor thickened, and there were no tumours in the lower conjunctival fornix. There were no enlarged glands elsewhere.

The spleen was not enlarged. The patient had not had any complaint but he had noticed that his face had broadened definitely during the last twelve years. When asked if he had any explanation as to why this had occurred, he jokingly blamed it on beer of which I believe he takes a fair quantity. His general health has been very good. My colleague tells me that he has not had to attend him for anything during the last ten to twelve years although he has attended the rest of the family.

In this case there is nothing else of note except a rather interesting fact that a sister of the patient died a few years ago from Lymphadenoma.

Blood examination gave a normal picture:

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
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<tbody>
<tr>
<td>Haemoglobin</td>
<td>100%</td>
</tr>
<tr>
<td>Red Cells</td>
<td>5,200,000</td>
</tr>
<tr>
<td>White Cells</td>
<td>8,000</td>
</tr>
</tbody>
</table>

The Differential Count showed a normal relation of the various white cells:

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphs</td>
<td>68%</td>
</tr>
<tr>
<td>Large and Small Mononuclears</td>
<td>28%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>4%</td>
</tr>
</tbody>
</table>

There were no myelocytes.
The case has since passed out of my care on the return of my colleague, but I insert these few notes to show how a case of Mikulicz's Disease can occur without any inconvenience to the patient, and without even causing him to consult a physician. The photographs were taken to illustrate the appearance of the patient. No treatment has been applied.
CASE 5.

Showing broadening of the face due to enlargement of the parotids.

Fig. 14a.

Fig. 14b.
The foregoing cases illustrate the various types of Mikulicz's Disease and Mikulicz's Syndrome that may be met with.

Case One is very interesting in that there is a suggestion of some septic absorption or some infective process being at work - the patient's constitutional symptoms at first suggesting some hidden focus of sepsis being present before any signs of enlarged glands were noted. There appeared first, signs of conjunctival irritation before tumour formation was noted, and definite enlargement of the lachrymal glands followed.

The plica semilunaris was also enlarged and thickened and as has already been noted in the pathological discussion, this structure contains lachrymal glands. Following this the enlargement of the parotid glands took place.

With regard to the suggestion of septic absorption a notable fact was that on both occasions when septic teeth were removed, the lachrymal enlargement was definitely exacerbated, the colour also becoming very much more angry.

Regarding the treatment for this case the remarkable recovery which followed the use of X-rays was striking.

The main symptoms that this patient complained of were firstly the disfigurement, secondly the irritation caused by the actual increase in size of the tumour in the lower
conjunctival fornix, which caused entropion, and also
difficulty in reading, which the Ophthalmic Surgeon found
was due to astigmatism in the horizontal axis, and which
cleared up after the lachrymal swelling had subsided.

**Case Two** illustrates the type that one frequently
meets with in the literature associated with irido-cyclitis.
From the description of her original attack one might
almost class her case amongst those cases of sialodochitis
described in Greig. (92)

**Case Three** shows the syndrome occurring in the
case of a lymphadenoma, clearing up under X-ray treatment
but with recurrence probably causing death a year or two
later.

**Case Four.** This was a case of Mikulicz's Disease
which responded again very well to X-ray treatment, but
unfortunately the patient died of an acute Nephritis after
definite improvement from the conditions for which she first came
under observation.

**Case Five** illustrates a type causing little or no
inconvenience to the patient and going on for some years
without his feeling any need to call in medical advice about
it. This was not under the care of the writer for a long
enough period to institute any treatment, but investigation shows no sign of lymphadenomatous or leukaemic condition, although the interesting note is made that a sister died from a lymphadenoma a year or two ago.
SUMMARY.

In the foregoing pages an attempt has been made to review available published cases of Mikulicz's Disease, and Syndrome, from the original description of Mikulicz himself down to the present time. One or two cases previous to Mikulicz's report have been included.

The first description of the disease was very full, so thorough indeed that only a little has been added to our knowledge in the intervening period. We have found that in the pathology of this condition, there is a massive infiltration with small round cells; in some cases appearance of a definite granulomatosis, in others a lymphadenomatous condition and in yet others definite leukaemia. In certain cases tuberculosis has been associated and even tubercle bacilli found in the tumour, and again syphilis has been shown to be associated in quite a number of cases. Sarcoma has also been responsible for a few cases, but these are not usually symmetrical in distribution. Cases associated with plumbism, iodism and one in which gout was said to be the cause have been noted, and a few show associated endocrine disturbance with improvement on treatment of the underlying lack of hormones. Besides these a number have been reported occurring in families in which various members of the family and of different generations have shown the syndrome to be
present. We can state that the disease is not a true hypertrophy of the gland tissue, but an infiltration with small round cells or hyperplasia of the lymphoid tissue normally present in the lachrymal and salivary gland structures.

There has not been found one definite causation which would reproduce the disease in a series of cases. Therefore we can only say that the condition is a clinical entity and as the pathology varies slightly, and the syndrome can occur in two or three different diseases, we cannot define it as a pathological entity.

Various classifications have been attempted, all of them useful, but any classification is necessarily arbitrary whilst the knowledge of the disease is not complete (even the processes at work in the various diseases in which Mikulicz Syndrome is found are not yet fully understood). However, such classifications are helpful in summarizing the present state of knowledge, and therefore such schemes will alter if and when any new facts are brought to light. With this in mind the following headings summarizing the various types of the condition are suggested:-

A. MIKULICZ DISEASE "PROPER". In which we get bilateral enlargement of the lachrymal, and/or salivary glands, without any enlarged lymph nodes or alteration of the blood picture. Certain cases referred to previously
as "formes frustes" may be included herein, though not perhaps bilateral. In this group also the familial or hereditary cases would be included.

B. **GRANULOMATOUS CONDITIONS.** Tuberculosis, Syphilis and Lymphadenoma.

C. **LYMPHOSARCOMA.**

D. **LEUKAEMIA.** (The term pseudoleukaemia is avoided here on account of the fact that it is somewhat doubtful in the minds of many that there is any condition to which this term may properly be applied).

E. **VARIOUS TYPES.**

E1. **Toxic,** plumbism, iodism, ? gout and cases of uveo-parotitis.

E2. **Endocrine disturbances.**

Five cases have been considered in detail, three of these have actually been observed by the writer, and the notes and photographs illustrating the other two have been kindly supplied by physicians who have personally observed them. These cases illustrate various types of the disease or syndrome with which one may meet.

Case 1 would fall into the group Mikulicz Disease "Proper" and shows the striking improvement following radiation with X-rays. (Group A).

Case 2. The type associated with irido-cyclitis. (Group E).

Case 3 shows the syndrome occurring in a case of lymphadenoma. (Group B).
Cases 4 and 5 would come under the heading of Mikulicz Disease "Proper." (Group A).

An attempt has been made graphically to illustrate the occurrence according to age groups and also to tabulate the various groups with regard to prognosis. For this purpose the groups have been simplified into three main headings.

First, cases with enlargement of the lachrymal and/or salivary glands, but with no lymph gland enlargement and with no blood change. This would include all the cases in Group A supra, also all the cases in Group E. The second group under which these results have been tabulated were those in which there was associated with the lachrymal and salivary gland enlargement, enlargement of lymph glands including spleen, but with no alteration in the blood picture. Groups B and C would fall under this heading. The third large group for this purpose was one in which associated with the lachrymal and salivary enlargement, there was enlargement of lymph glands with associated blood changes. This would include all those cases in Group D.
CONCLUSIONS.

1. The condition is met with most frequently in adults in the third decade to the fifth decade of life. (Though in leukaemic cases the largest percentage is in the first decade of life).

2. In Mikulicz's Disease "Proper" there is strong evidence of an infective process at work.

3. No definite evidence of an evolution from a simple lymphoma through pseudoleukaemia (sic) to leukaemia and further to sarcoma has been made out.

4. The diagnosis of the condition is easy, but it is essential in every case to differentiate the group into which the patient falls.

5. The symptoms are the definite enlargement of the glands, causing disfigurement and sometimes interference with function due to pressure on surrounding structures. There may be some slight general constitutional disturbance, but often none at all.

6. With regard to treatment, exposures to X-rays with or without Radium, or Radium alone, appear to be the most successful therapeutic measures. Potassium iodide seems to be the drug most successfully used, but the results are not so striking with this form of treatment.
7. **Prognosis in Group A.** This is good as regards both life and recovery from the condition.

Group B. This will depend on the response to treatment of the general conditions causing the syndrome. In Groups C and D the prognosis is poor.

In Group E, the prognosis depends on the removal of the cause of the toxic condition, and in E 2 the administration of the appropriate endocrine which is lacking, or treatment with a view to mitigating symptoms arising from such lack, e.g. certain cases associated with diabetes were improved with a dietetic regime.
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<th>Author</th>
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<tr>
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