SJÖGREN'S DISEASE AND RHEUMATOID ARTHRITIS

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It is widely held that rheumatoid arthritis is a generalized disease in which joint symptoms are merely the most prominent feature. In support may be cited lymphocytic infiltrations and wasting of muscles, subcutaneous nodules, psoriasis, pigmentary disturbances and atrophy of the skin, changes in plasma proteins and abnormal flocculation tests, anaemia, iritis, and manifestations of general toxaemia, all of which are well known in association with the joint changes.

In view of the effects of cortisone and ACTH on many diseases which affect connective tissues, it is possible that their action in rheumatoid arthritis is due to a similar effect, and that an abnormality of connective tissue throughout the body underlies the variety of lesions which may be associated with this disease. It may be that some local stimulus such as infection, trauma, vascular disturbance, or temperature change, acting in the presence of such a generalized tissue abnormality, accounts for the manifestations in a particular case.

Further evidence supporting this view, is the observed association of arthritis of the rheumatoid type with changes in the tissues of the cornea, lacrimal and salivary glands, buccal mucous membrane, teeth, and skin.

The association of kerato-conjunctivitis sicca and joint changes was first noted by Houwer (1927), and confirmed by Isikowitz (1928); but after the publication of the detailed report of nineteen cases by Sjögren (1933) and his subsequent papers (1935, 1938) in which oral, parotid, and skin changes were also noted, the syndrome has become known as Sjögren's disease.

Weber (1945) and Weber and Ellman (1949) have reviewed the literature and described further cases, one of which also showed changes in the respiratory tract. Stenstam (1947) and Holm (1949) have described detailed investigations in a large series of cases in Sweden.

Sjögren considered that the syndrome was a disease *sui generis*, but Weber thought the manifestations were merely the local symptoms of a general disease. In support of the latter concept, may be quoted Holm's finding that 53 of 440 patients with rheumatoid arthritis had objective evidence of kerato-conjunctivitis sicca, although many of the 53 did not complain of symptoms related to the eyes. He infers that the ocular changes are relatively common in ordinary cases of rheumatoid arthritis. The objective tests for kerato-conjunctivitis sicca used

by Holm were the same as those used by Sjögren—the rose bengal staining method to demonstrate denudation of the corneal epithelium, and the test described by Schirmer (1903) to assess the efficiency of lacrimal secretion.

If Holm's conclusion can be substantiated, it provides further evidence that the joint symptoms of rheumatoid arthritis are local processes superimposed upon a tissue disorder widespread throughout the body.

We have carried out Schirmer's test in a small series of rheumatoid arthritis patients and the results are reported below, together with the clinical and autopsy details of a case of Sjögren's disease showing unusual changes in the renal tracts.

Investigation

Material.—The series comprised 47 women and fifteen men, aged 17 to 72. All had typical manifestations of rheumatoid arthritis. The control group also comprised 47 women and fifteen men, of comparable ages, who were hospital in-patients suffering from non-rheumatic illnesses. None of the subjects suffered from ocular symptoms.

Method.—Strips of red litmus paper 5×33 mm., were folded at right angles 3 mm. from one end, and the folded end was tucked into the outer canthus of the lower conjunctival sac. The length of paper which became wet in 5 min. was measured and the average for the two eyes recorded. Litmus paper from the same batch was used throughout.

Schirmer, Sjögren, and Holm all considered a moistened area 15 mm. long to be the lower limit of normal.

Results.—These are shown in the Table. Of the rheumatic subjects, seventeen of the 47 women, and three of the fifteen men had deficient lacrimal secretion by this standard, compared with four of 47 women and one of fifteen men in the control group. The observations show a significant difference between the rheumatic and non-rheumatic subjects ($\chi^2 = 9{\cdot}8$, D.F. $= 1$, $P < 0{\cdot}01$) and thus support the conclusions of Holm. The length of paper moistened bore no relation to age.

TABLE

RESULTS OF SCHIRMER'S TEST IN TWO SERIES OF 62 CASES

Result (mm.)	Cases	
	Rheumatoid	Control
0-4	2	1
5-9	8	1
10-14	10	3
15-19	9	9
20-24	9	11
25-29	14	25
30	10	12

Report of One Case

Clinical Observations.—The patient (R.I. No. 18667/43) was a married woman who was first admitted to the Radcliffe Infirmary in July, 1948, at the age of 28. Her presenting symptoms were pain and stiffness of the joints for 3 months. The condition had started in her right knee and had spread to the left knee, shoulders, elbows, wrists, and fingers.

For the same period she complained of weakness and pain in the muscles about the affected joints. Her general health had deteriorated, she was pale, had lost weight, and was always tired. For 10 years she had noticed excessive thirst and polyuria. The thirst was associated with chronic dryness of the mouth so that she had to drink copiously with her meals in order to masticate her food. She associated this with a series of parotid swellings, the first of which occurred at the age of 19 on the right side. There had been seven further swellings on the left side, the last having occurred in 1946. The first swelling was thought to be suppurative and was incised, but the rest all subsided spontaneously.

She did not complain of any ocular symptoms, but on direct questioning said she had occasional attacks of soreness of the eyes, and then volunteered that she was frequently troubled with sticky mucus between the lids.

There were no other symptoms referable to the alimentary or urinary systems, and none referable to the respiratory, cardiovascular, or central nervous systems. Her menstrual periods were normal and did not appear to be associated in any way with her symptoms.

She had had two pregnancies. The first (1941) was normal; the second (1947) was complicated by puerperal septicaemia. The arthritis commenced 8 months after the second pregnancy. There had been no previous rheumatism, renal disease, or other significant illness. The family history was not relevant.

On examination she was a pale, thin, tired-looking woman, with dry skin and dry falling hair. There was tenderness and fusiform swelling of the proximal interphalangeal joints. She could barely close her fist. During the period of observation, varying degrees of pain, swelling, stiffness, and restricted movement occurred in the wrists, elbows, shoulders, and knees. There were several subcutaneous nodules over the right ulnar surface and the right patella.

All her teeth had been extracted some years previously. There was some redness and smoothness of the mucous membrane of her tongue, but no apparent abnormality of the buccal mucous membrane nor of the salivary glands. Her eyes appeared normal. There were enlarged lymph glands, about 1 cm. in diameter in both axillae, but none elsewhere.

The thyroid gland was not palpable, and there was no evidence of thyroid dysfunction. Blood pressure was normal (120/65 mm.) and there was no abnormality of cardiovascular, respiratory, alimentary, or central nervous systems. Liver, spleen, and kidneys were not palpable.

Investigations showed a moderate hypochromic anaemia (haemoglobin 9·6 gm. per 100 ml.), leucocytes 9,000 per c.mm., erythrocyte sedimentation rate (Westergren) 68 mm. in one hour. Urine contained 20 mg. protein per 100 ml., but no other abnormal constituents. Blood urea was 46 mg. per 100 ml., plasma protein 7·5 gm. per 100 ml. (albumin 3·6, globulin 3·9), serum alkaline phosphatase 6 King Armstrong units.

The clinical picture was that of mild rheumatoid arthritis associated with rather more constitutional disturbance than one would have expected from the joint changes. In view of the recurrent parotid swellings, dryness of mouth, dry skin, dryness of eyes, dental deficiency, and arthritis, she was considered to be a case of Sjögren's disease. During her stay in hospital there was some improvement in her general condition, but the arthritis remained unchanged and she was discharged to continue under observation as an out-patient.

For the next 2 years there was little real change in her condition. For most of the time she was tired and lacking in energy, and her arthritis never completely settled down. Haemoglobin varied from 8·8 to 13·1 gm. per 100 ml., and erythrocyte sedimentation rate from 8 to 42 mm. in one hour. The proteinuria increased after her discharge, and varied from 40 to 90 mg. per 100 ml. No formed elements were found in her urine. In April, 1949, blood urea was 38 mg. per 100 ml.

In May, 1949, intravenous pyelogram (Figs 1 and 2) was carried out by Dr. J. L. Boldero, of the *X*-Ray Department of the Radcliffe Infirmary, to whom we are indebted for the following report:

> Preliminary renal *x* rays: Multiple calcified glands in the lower abdomen. There are punctate calcifications overlying both kidney shadows (Fig. 1).
>
> Excretion urography: Good concentration of dye on both sides. The presence of the punctate calcified shadows is closely associated with all the calyces (Fig. 2). The aetiology of the calcification is quite obscure.

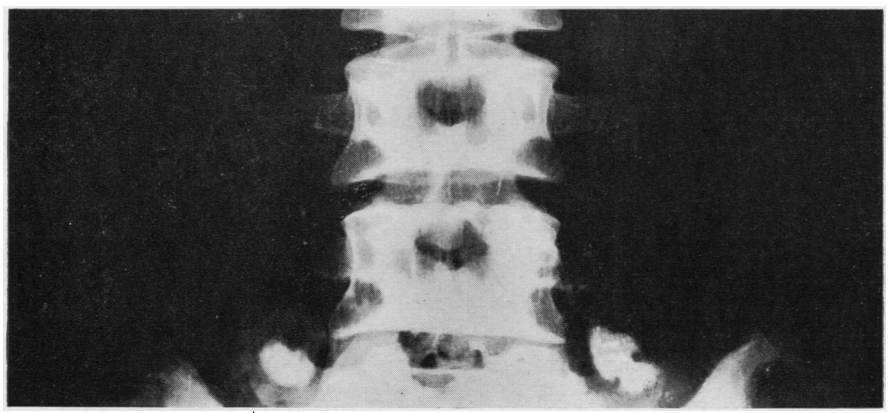

FIG. 1.—*X* ray taken during life, showing small calcified deposits in pyramids of both kidneys.

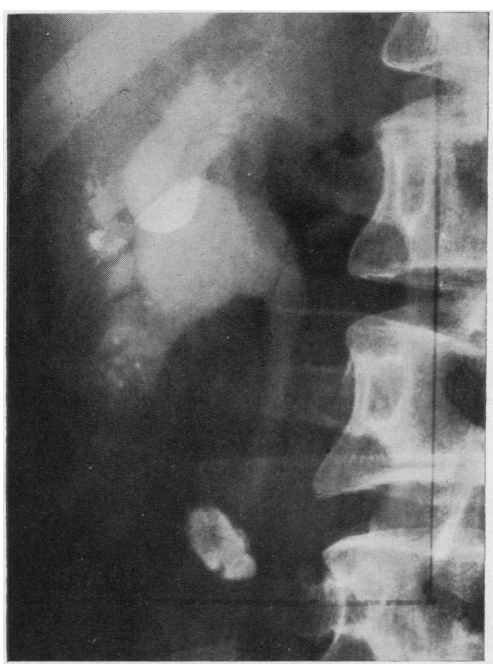

FIG. 2.—*X* ray taken during life, lateral view.

At this time her serum phosphate was 4·5 mg./100 ml., calcium 7·8 mg./100 ml., and phosphatase 7 King-Armstrong units. Blood pressure was 110/70 mm.

Thirst and dryness of the mouth also ran a variable course, and for periods her salivary secretion appeared to be normal. There was no recurrence of parotid swelling. A series of Schirmer's tests carried out over 12 months gave the following results:

Date	*Average length moistened (mm.)*
15.7.49	6
14.9.49	15
26.9.49	16
23.11.49	8
5.7.50	5

Treatment during this period was along symptomatic lines, with physiotherapy, salicylates, ferrous sulphate, and a short period at a spa.

In June, 1950, the patient complained of increasing joint symptoms, especially in the shoulders and neck, and of increasing fatigue; she was noted to

have lost about 4 lb. weight in the previous 3 months. During the next month symptoms persisted and she lost a further 5 lb. Physical examination on several occasions showed a chain of tender lymph glands over the anterior border of the left trapezius muscle but no other fresh abnormality. Erythrocyte sedimentation rate 44 to 50 mm. in one hour, haemoglobin 11·8 gm./100 ml., white blood count, 4,500 c.mm., urinary protein 40 mg./100 ml. Chest *x* ray showed no lesion.

This was the last time we saw the patient alive. Before her next appointment at the out-patient department was due she developed an acute attack of gastro-enteritis with fever, vomiting, and diarrhoea, and was admitted to the local cottage hospital. Symptoms persisted, and she developed pleural and pericardial friction rubs. Re-admission to the Radcliffe Infirmary was arranged, but on the same day her condition suddenly deteriorated, and she died on October 3, 1950.

Autopsy Findings.—*Post-mortem* examination was performed 24 hours after death. The body was that of an emaciated woman appearing older than 30 years. There was slight fusiform swelling of the proximal interphalangeal joints of both hands. The skin was natural and no subcutaneous nodules were found.

No lesions were found in the skull, meninges, brain, or cerebral vessels, and there were no lesions in the middle ears, mastoid cells, or paranasal sinuses.

The mouth was edentulous. The tongue was red and dry but showed no ulceration. There was some ulceration of the soft palate. The lower respiratory passages appeared natural but contained some viscid muco-pus.

Both lungs were adherent on all surfaces to the chest wall, due to the presence of a thin layer of plastic fibrinous exudate. The visceral pleura did not appear congested. The major part of both lungs was well aerated, but there were small patches of collapse along the lower margin of the lower lobes. Emphysematous bullae up to 1 cm. in diameter were scattered over the surfaces of both lungs. There was no excess of fluid on section. About half a dozen small areas of consolidation (up to 3 mm. in diameter) were found in the periphery, mostly in the right lung. Their margins were dull red and the centres yellowish. There was no gross abscess formation.

The only change in the cardiovascular system was a dry fibrinous pericarditis.

Only the left parotid gland was examined and this appeared smaller and more fibrinous than usual. The oesophagus, stomach, and small intestine appeared natural. The transverse colon showed some punctate ulceration. The liver appeared paler than usual with some fatty change. The gall bladder, bile ducts, and pancreas appeared natural.

The kidneys were both slightly smaller than natural. The cut surface showed some pallor, and the cortex was poorly differentiated from the medulla. The pyramids contained numerous yellowish-brown, stony-hard concretions up to 1 mm. in diameter. The pelves contained no stones and the rest of the urogenital tract appeared natural.

The breasts were atrophic. The spleen was slightly enlarged and the follicles prominent. There was slight generalized lymph-gland enlargement.

The left knee contained a slight excess of fluid and the synovium was thickened and congested.

Histology.—The findings are grouped into:

(*a*) Those related to the terminal illness with pneumonia and renal failure.
(*b*) Those related to the chronic condition in the lacrimal and salivary glands, joints, and muscles.

(*a*) The kidneys show generalized tubular dilatation. There are numerous narrow wedge-shaped lesions in the cortex, in which the glomeruli show capsular fibrosis and

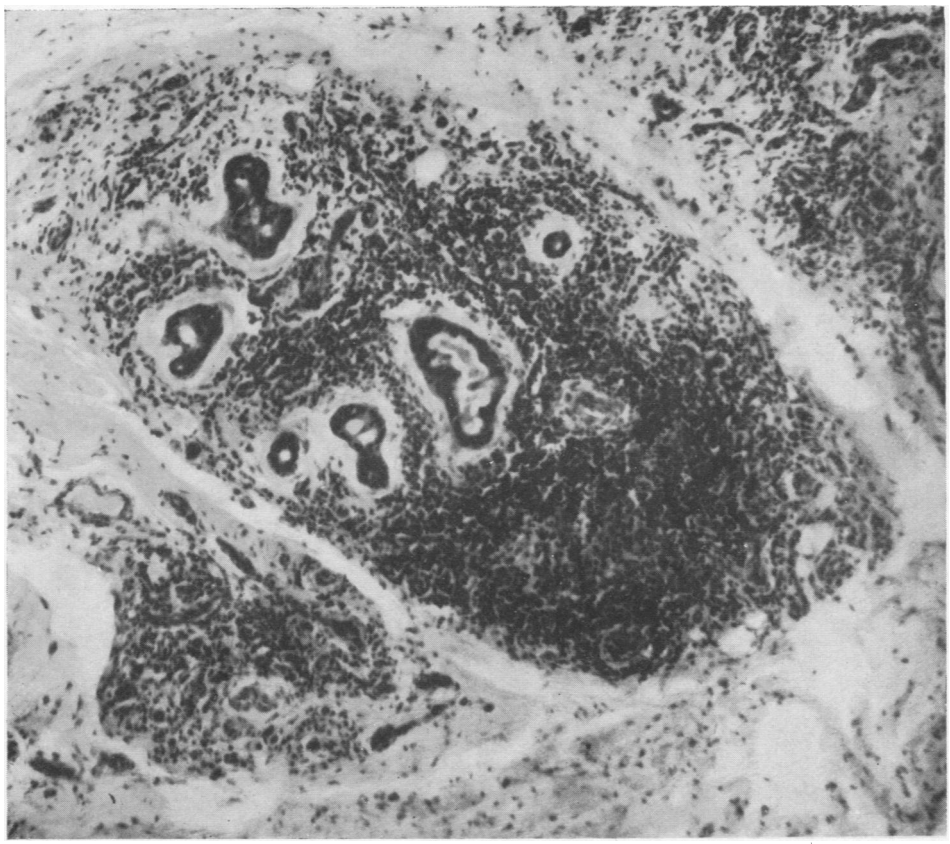

FIG. 3.—Section of lacrimal gland taken at *post-mortem*, showing extensive infiltration with lymphocytes and plasma cells with disappearance of gland acini. The ducts are relatively unaffected. There is also some perilobular fibrosis. Haematoxylin and eosin ×120.

obliteration, and there is fibrous replacement of the tubules with some lymphocytic and plasma-cell infiltration. The concretions in the medulla lie in the collecting tubules. There are no vascular lesions.

The pleura and pericardium show subacute inflammatory change with exudation of fibrin as seen in uraemia. Most of the major bronchi show severe subacute inflammatory change. The areas of consolidation are related to branch bronchi and consist of acute inflammatory exudation with central necrosis.

The gastro-intestinal tract shows some lymphocytic and plasma-cell infiltration of the mucosa. Autolysis prevents detailed examination, but there appear to be no underlying chronic changes. There is some lymphocytic and plasma-cell infiltration of the portal tracts of the liver, and some centrilobular fatty change.

(*b*) The right lacrimal gland (Fig. 3) shows chronic inflammatory change. This is patchy in distribution, and resembles that described by Sjögren (1933). Some of the lobules appear natural, others show a moderate degree of lymphocytic and plasma-cell infiltration between the acini. Many acini in these lobules are made up of irregular pale cells which have lost their orderly arrangement. Mitoses are seen occasionally but there are no cell inclusions. In the most severely affected lobules the acini have disappeared, leaving only the ducts surrounded by lymphocytes and neutrophile leucocytes and some young

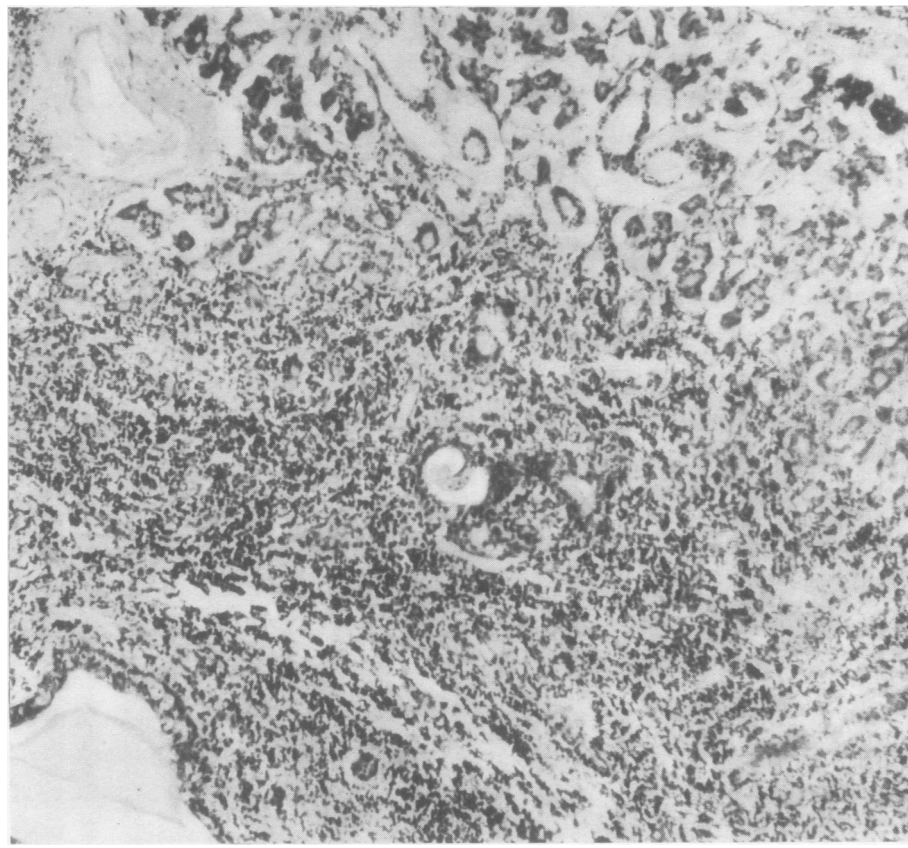

FIG. 4.—Section of parotid gland taken at *post-mortem*, showing similar extensive replacement of gland acini by lymphocytes and plasma cells. Haematoxylin and eosin ×120.

fibrous tissue. Some of the ducts are distended with inspissated material. About a third of the gland substance appears capable of normal function. The overlying conjunctiva shows cellular and pericellular oedema of the stratified epithelium, with some cyst formation and dilatation of the underlying lymphatics. This change was described by Sjögren in his biopsy material.

Sections of the parotid and submandibular glands show changes similar to those in the lacrimal gland but more severe and more extensive. There is advanced fibrosis and some of the lobules show replacement by fatty connective tissue. The parotid (Fig. 4) shows many cystic spaces lined by flattened-duct epithelium and filled with inspissated mucus.

The submucous glands of the nasal mucosa, pharynx, tongue, trachea, and bronchi show similar changes which are most marked in the soft palate (Fig. 5), where areas of epithelium have been replaced by necrotic material and poorly formed granulations. The mucosa of the paranasal sinuses is natural and there are also isolated lobules of mucus-secreting glands showing no abnormality in otherwise severely affected areas. The mucosa of the pharynx shows a range of changes ending in ulceration. There is prolongation of the rete pegs with acanthosis and considerable variability in the basal epidermal cells with some mitotic activity, and in the ulcerated areas there has been a disappearance of the superficial epithelium and irregular regeneration of the basal cells. In the pharynx the

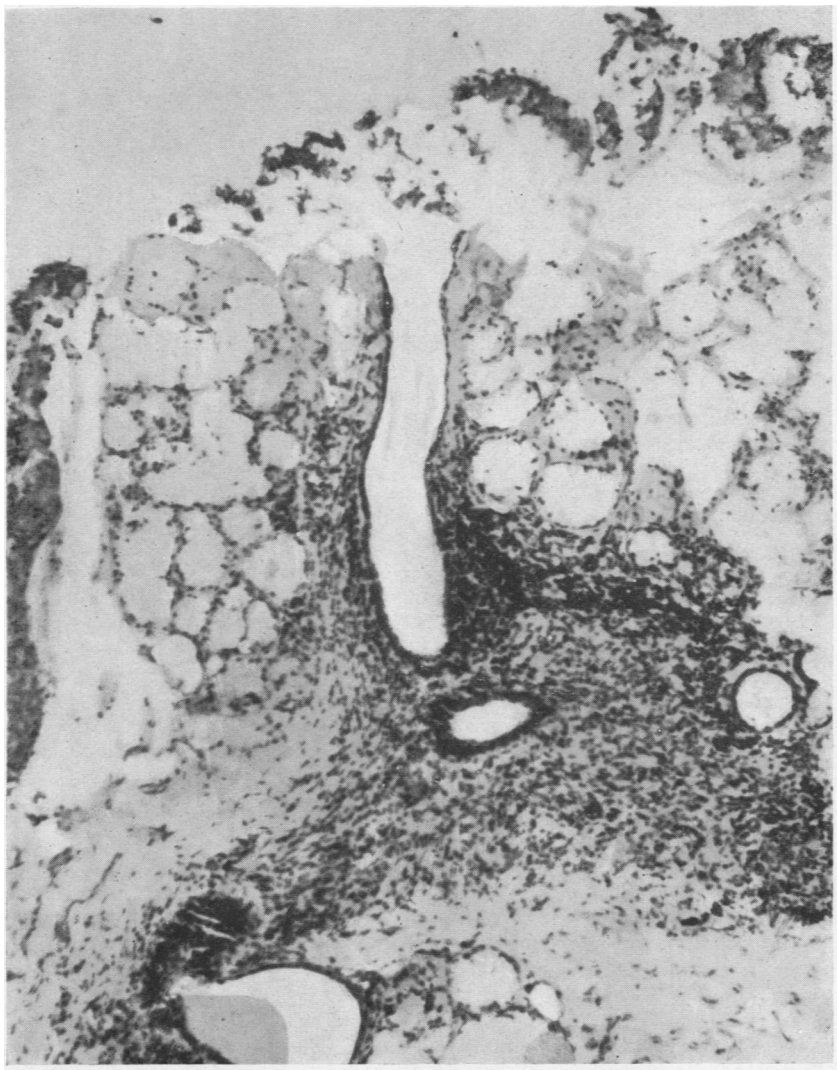

FIG. 5.—Section from soft palate taken at *post-mortem*, showing necrosis of superficial mucosa and inflammatory changes in submucous glands. Haematoxylin and eosin ×120.

ulcerated areas are covered by a fibrinous membrane in which there is a mixed bacterial and fungal flora. In the non-ulcerated areas, best seen in the tongue, there is a lymphocytic proliferation of the subepithelial connective tissue. The glands of the uterine cervix are natural. The thyroid, pancreas, and skin show no abnormality.

Section of the left fourth interphalangeal joint shows some marginal erosion of the joint cartilage, with the formation of a relatively acellular fibrous pannus. Similar fibrosis without marked inflammatory cell infiltration is seen in the synovium. The synovium of the knee joint shows oedema and proliferation of the villi, with a minor degree of lymphocyte and plasma-cell infiltration.

A section from the left quadriceps extensor muscle of the knee shows perineural and perivascular foci of lymphocytic and plasma-cell infiltration, with some proliferation of fibrous tissue.

The lymph nodes show moderate medullary and sinus proliferation, and in a node from the right cervical chain there is medullary reticulum-cell proliferation with some binucleate forms.

The cerebrospinal fluid urea content was 145 mg./100 ml. The renal medullary concretions were composed of calcium and magnesium phosphate.

Summary of Autopsy Findings.—It is evident that the patient died with uraemia and aspiration pneumonia with abscess formation, probably precipitated by an attack of non-specific enteritis. The kidneys were the site of a chronic low-grade pyelonephritis which had not been severe enough to cause renal failure until the final acute illness with its disturbance of fluid balance.

The cause of the concretions in the tubules remains obscure. They had been present for many months if not years, and in view of the history of polydipsia and polyuria, cannot be related to dehydration. There was no clinical, biochemical, or autopsy evidence of parathyroid tumour.

The changes described by Sjögren were present in the lacrimal glands and the conjunctiva, and were even more marked in the salivary glands and respiratory mucous membrane. Histological changes characteristic of rheumatoid arthritis were present in the joints. Although Weber (1945) suggested that the chronic inflammatory process may also occur in the pancreas, thyroid, skin, colon, and genital tract, there was no evidence of involvement of these tissues in the present case.

Discussion

Our observations have confirmed those of Holm (1949) that patients suffering from rheumatoid arthritis tend to have a deficiency of lacrimal secretion even though there are no symptoms referable to the eyes.

It would be interesting to examine the lacrimal and salivary tissues in a series of rheumatoid arthritis cases coming to autopsy, to determine whether the histological changes are also present in asymptomatic cases. It may be that these non-specific inflammatory lesions occur in these glands and respiratory tissues, as they do in skin (Curtis and Pollard, 1940), muscles (Freund and others, 1945; Steiner and others, 1946; Gibson and others, 1946), tendons (Kellgren and Ball, 1950), and subcutaneous tissues (Bennett and others, 1940). The changes described above resemble in many ways those reported by the above workers: the lymphocytic and plasma-cell infiltrations, the disorganization of the underlying tissue with necrosis in some areas, and the rather feeble fibrous tissue response.

Further evidence that the lacrimal and salivary lesions are aetiologically related to the rheumatoid process is the clinical observation that the ocular and oral signs in a case of Sjögren's disease cleared up along with the joint lesions on treatment with ACTH, and relapsed again on cessation of therapy (Stephens, 1950).

The relationship of the chronic renal lesion to the salivary, lacrimal, and respiratory lesions in our patient is not clear. Probably the chronic pyelonephritis was quite coincidental, and the tubular calculi were secondary to the chronic infection. The possibility of a more direct relationship, however, cannot be excluded.

Summary

(1) Clinical and autopsy observations in a case of Sjögren's disease are described.

(2) An investigation of the lacrimal secretion in a series of patients confirms

the observations of Holm (1949) that there is a tendency to deficient secretion in rheumatoid arthritis.

(3) The importance of the lacrimal and salivary lesions is discussed in relation to the aetiology of rheumatoid arthritis.

Our thanks are due to Dr. F. V. Squires of Wantage for details of the patient's final illness and for his co-operation in arranging for the autopsy, and to Dr. A. H. T. Robb Smith for his advice on the histological examination. We are also indebted to Dr. R. H. Cowdell of the Department of Pathology, Radcliffe Infirmary, for the photomicrographs.

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La Maladie de Sjögren et l'Arthrite Rhumatismale

Résumé

(1) On présente l'observation, y compris les résultats d'autopsie, d'un cas de maladie de Sjögren.

(2) L'étude de la sécrétion lacrymale chez un groupe de malades confirme les observations de Holm (1949) constatant que dans l'arthrite rhumatismale cette sécrétion tend à diminuer.

(3) On discute l'importance des lésions lacrymales et salivaires par rapport à l'étiologie de l'arthrite rhumatismale.

La Enfermedad de Sjögren y la Artritis Reumatoide

Sumario

(1) Se presenta un informe clínico y de autopsia de un caso de enfermedad de Sjögren.

(2) El estudio de la secreción lacrimal en un grupo de enfermos confirma las observaciones de Holm (1949) de que en la artritis reumatoide esta secreción tiende a ser deficiente.

(3) Se discute la importancia de las lesiones lacrimales y salivarias en relación con la etiología de la artritis reumatoide.