

- PETRI, S. (1937).—*Acta Med. Scand.*, Vol. XCIII, p. 450.
- PIRIE, A. (1943).—*Brit. Jt. Ophthalm.*, Vol. XXVII, p. 291.
- POCK-STEEN, P. H. (1939).—*Jt. Amer. Med. Assoc.*, Vol. CXIII, p. (Abstract).
- POLLAK, H. (1943).—*Trans. Ophthal. Soc. U.K.*, Vol. LXIII, p. 69.
- RHOADS, C. P. (1941).—*Jt. Nat. Cancer Inst.*, Vol. I, p. 511.
- SEBRELL, W. H. and BUTLER, R. E. (1939).—*Public Health Rep.*, Vol. LIV, p. 2882.
- SHAPIRO, N., SCHIFF, L., BLOCH, H. S., GARBER, E. S. and HANNAHER, M. J. (1944).—*Gastroenterology*, Vol. II, p. 121.
- SIMONSON, E., ENZER, A., BAER, A. and BRAUN, R. (1942).—*Jt. Indust. Hyg. Tox.*, Vol. XXIV, p. 83.
- SMITH, S. G. and MARTIN, D. W. (1940).—*Proc. Soc. Exp. Biol. Med.*, Vol. XLIII, p. 660.
- STANNUS, H. S. (1912).—*Trans. Soc. Trop. Med. Hyg.*, Vol. V, p. 112.
- (1937).—*Trop. Dis. Bull.*, Vol. XXXIV, p. 183.
- (1940).—*Lancet*, Vol. I, p. 352.
- (1944).—*Brit. Med. Jt.*, Vol. I, p. 103.
- STEWART, C. P. (1941).—*Edin. Med. Jt.*, Vol. XLVIII, p. 217.
- SYDENSTRICKER, V. P., SEBRELL, W. H., CLECKLEY, L. M. and KRUSE, H. D. (1940).—*Jt. Amer. Med. Assoc.*, Vol. CXIV, p. 2437.
- THOERELL, H. (1935).—*Biochem. Zeitschr.*, Vol. CCLXXIX, p. 186.
- VANOTTI, A. (1944).—*Schweiz. Med. Wochenschr.*, Vol. LXXIV, p. 309.
- VERMA, O. P. (1942).—*Ind. Med. Gaz.*, Vol. LXXVII, p. 646.
- WALDENSTRÖM, J. and HALLEN, L. (1938).—*Acta Med. Scand.*, suppl. 90, pp. 380, 398.
- WALDENSTRÖM, J. and KJELLBERG, S. R. (1939).—*Acta Radiol. Scand.*, Vol. XX, p. 618.
- WEDER, A. (1943).—*Ibid.*, Vol. LXXIII, p. 1354.
- WHITBY, L. E. H. and BRITTON, C. J. H. (1944).—*Disorders of the blood*. London.
- WILKINSON, B. P. and KING, A. (1944).—*Lancet*, Vol. I, p. 528.
- WINTROBE, M. M. (1942).—*Clinical Hematology*. London.
- WITTS, L. J. (1931).—*Guy's Hosp. Rpts.*, Vol. LXXXI, p. 193.
- YUDKIN, S. (1941).—*Brit. Jt. Ophthalm.*, Vol. XXIV, p. 231.
- (1941).—*Lancet*, Vol. II, p. 787.

SJÖGREN'S SYNDROME, ESPECIALLY ITS NON-OCULAR FEATURES*

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CHRONIC inflammatory changes in the parotid glands, usually without superadded abscess-formation but with recurrent exacerbations, leading to permanent changes in the glands in question—enlargement, sclerosis, atrophy, in irregular combination—is sometimes associated with similar changes in the other salivary glands, and more or less dryness of the mouth, also with similar chronic inflammatory changes in the lacrimal glands—though usually without obvious clinical enlargement—and with keratoconjunctivitis sicca. Starting from the ocular side Henrik Sjögren

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of Jönköping (1933 and 1935), from exhaustive study of his own cases and of earlier scattered literature, succeeded in establishing the existence of a syndrome, which in its complete form includes kerato-conjunctivitis sicca, xerostomia, rhinitis sicca, pharyngitis sicca, and laryngitis sicca, but which is far more often incomplete. This syndrome for convenience I would (Weber and Schlüter, 1937), following von Grosz (1936), term Sjögren's syndrome. As Sjögren himself points out, there are, of course, earlier observations bearing on the subject. For instance, Duke-Elder (1930), writing on keratitis sicca (his second group) occurring spontaneously in women after the climacteric, mentioned that in many of the cases a somewhat similar defect in secretion involved the salivary glands of the mouth. He said also that in some cases the sweat glands of the skin were likewise involved, but to this I will refer further on. The clinical onset of Sjögren's syndrome is intermittent and mostly very insidious.

Sjögren's main conclusions (1933, 1935, 1938) were as follows:—

Kerato-conjunctivitis sicca is a local symptom of a general syndrome or disease, to which females are far more predisposed than males. In the complete syndrome the most important part is diminution or cessation of secretion from the lacrimal and salivary glands as also of the secretion from the glands of the upper air passages. The diminution of secretion is caused by a chronic inflammation of the glands in question, which leads to atrophy and sclerosis of the glandular parenchyma. The mucous membrane changes—for instance, chronic oedema and alteration or atrophy of the epithelium, as observed microscopically in cases of kerato-conjunctivitis sicca—are secondary to the dryness from diminution of glandular secretion. In this connection it should be noted that Duke-Elder (1930) recorded a case of "keratitis sicca" resulting from congenital aplasia of the lacrimal glands.

According to the group of glands affected we may get kerato-conjunctivitis sicca, xerostomia, rhinitis sicca, pharyngitis sicca or laryngitis sicca. All these various groups of glands may be affected in the same individual, but usually the syndrome is incomplete and limited to one or more of the groups.

Clinical accompaniments of the syndrome may include: acceleration in the sedimentation-rate of the erythrocytes (as in other chronic infections); alterations in the blood-count (hypochromic anaemia), body temperature, and blood-sugar curve; arthritic symptoms of chronic infections (especially rheumatoid arthritis) type; and perhaps the presence of focal infection somewhere.

Sjögren thinks that, whether the primary cause of the syndrome be infective, toxic, allergic, or partly of endocrine nature, it is through the circulating blood that the change in the affected glands is excited. The question of whether other glands may be also

affected he leaves to future observation. By that, I take it, he refers mainly to the cutaneous (especially sweat) glands, but in certain cases (see below) it is possible that the acid-producing glands of the stomach may be involved. Test for pancreatic insufficiency would be also worth trying. In this regard some interesting data are given by M. and F. Cahane (1930) and in a paper by E. Flaum (1933). Experimental excision of the sub-maxillary glands in animals causes hyperglycaemia, whilst excision of the parotid glands causes hypoglycaemia and increase of hepatic glycogen. In rabbits ablation of all 4 salivary glands was followed in 2 or 3 days by increasing glycosuria. An insulin-like product has been extracted from the secretion of the sub-maxillary gland (Dodds and Dickens, Banting and Best). Injection of pure parotid extract caused diminution of blood-sugar. Flaum concludes that the parotid gland has an internal secretion which helps in regulating carbohydrate metabolism.

From Sjögren's histological investigations it appears that the chronic inflammatory changes may commence insidiously and be already present to some degree before the occurrence of any obvious clinical signs. Thus, the lacrimal glands may be microscopically affected before the occurrence of clinical keratoconjunctivitis sicca, and doubtless, the parotid glands may show microscopic changes before the occurrence of parotid swellings or xerostomia, as may also the glands of the mucous membrane of the nose, lips, pharynx and larynx.

The lacrimal glands in Sjögren's syndrome are, I gather, never clinically enlarged, and the recurrent swelling of salivary glands seems to be due to temporary obstructions from inflammatory swelling in the ducts.

Sjögren (1933 and 1943) stresses that, just as the dry mouth is associated with diminution in the salivary secretion, the keratoconjunctivitis sicca is associated with diminution in the lacrimal secretion. He concludes: "The morbid changes of the eye appear in consequence to find their simplest explanation in the fact that, owing to intense diminution or complete abolition of the lacrimal secretion, the conjunctiva itself is obliged to provide for the entire secretion of fluid. As the result of this a chronic oedema arises, which gradually leads to degeneration and atrophy of the epithelium." Surely this suggests an analogous explanation for secondary changes in the oral mucosa when they arise in cases of chronic xerostomia of any nature.

He suggests that cases of elderly women with dry mouth "aptyalism" or xerostomia, first described by Hutchinson (1888) and Hadden (1888), may be of the same nature as what we here term "Sjögren's syndrome."

According to E. and T. Dalsgaard-Nielsen (1937) keratoconjunctivitis sicca is almost limited to women over the age of

60 years. It is bilateral and characterised by hyperaemia of the conjunctivae, reduced tear secretion, thickening of the corneal epithelium, a sense of itching or burning, photophobia, reduced acuity of vision, dryness of the mouth, and hoarseness. In five of their seven cases there was a history of "rheumatism" of joints or muscles. In one of the two cases in which the temperature was investigated there was slight fever. In all cases onset was insidious and the course chronic and progressive. The authors regard the disease as due to a chronic infection of the vegetative nervous system, probably connected in some way with the sex function in women.

I will here shortly describe some cases which bear on the symptomatology of (complete and incomplete) examples of Sjögren's syndrome, and then I will discuss certain points in differential diagnosis.

Cases

Recurrent parotid swelling with moderate xerostomia and gastric achlorhydria.—The case, for which I am indebted to Dr. A. Schlüter, is that of a woman, aged 69 years, whom I first saw in May, 1936 (Weber and Schlüter, 1937). On that occasion both parotid glands were moderately enlarged and hard, the right somewhat larger than the left. There was definite xerostomia, the saliva tending to be somewhat stringy. The attacks of parotid swelling had commenced three years ago and in the first year of the illness involved the right side only. At first there had been only one or two attacks in the year, but in 1936 they became more frequent. They involved one or both sides, and lasted about a week. They were apparently not accompanied by fever or leucocytosis.

In May, 1936, the blood-count gave: haemoglobin 84 per cent.; erythrocytes 4,240,000; leucocytes 8,200 (eosinophils 5 per cent.; polymorphonuclear neutrophils 57 per cent.; lymphocytes 25 per cent.; plasma-cells 1 per cent.; monocytes 12 per cent.); slight anisocytosis. Fractional examination of gastric contents showed absence of free hydrochloric acid excepting after a subcutaneous injection of histamine. The blood sedimentation-rate was very slightly accelerated. Urine: nothing special, excepting slight excess of urobilinogen. The blood serum gave negative Wassermann and Meinicke reactions. Brachial blood-pressure: 155/85 mm. Hg. No kerato-conjunctivitis sicca or enlargement of lacrimal glands. No calculus seen by X-ray examination of the salivary glands. The patient had been edentulous since about 1918. Nothing special in the family history, excepting that the patient's mother suffered from asthma. When the parotid swellings first occurred in this case, mumps was thought of (as it was in many other cases).

Since May, 1936, the patient has had further attacks. In January, 1937, fractional examination of the gastric contents showed absence of free hydrochloric acid even after subcutaneous injection of histamine (the reaction for pepsin was slightly positive after the histamine). The patient has been lost sight of.

Recurrent parotid swelling with xerostomia, dryness of conjunctivae, achlorhydria, hypochromic anaemia, low blood-pressure, hypoglycaemia and Raynaud's phenomena.—For this case I am indebted to Dr. L. M. Rice. The patient, a thin woman, aged 40 years, unmarried (a brave individual who acted as a chauffeur formerly and does not worry more than necessarily about herself), was admitted to hospital for observation in July, 1936, when there was moderate parotid swelling on both sides (Weber and Schlüter, 1937). The history was that she had been subject to recurrent parotid swellings during the last 12 years, each attack lasting about 3 weeks. Almost always only one parotid has been affected at a time. During an attack the parotid region is painful and tender to pressure and at the height of the attack becomes red as if about to suppurate but an abscess has never occurred.

Dr. C. Markus kindly examined the eyes and found a condition of "keratitis filiformis," that is to say, what Sjögren terms "kerato-conjunctivitis sicca"; the fundi, tension and sensation were normal; the visual disturbance complained of was due solely to the corneal epithelial changes. The eye trouble rapidly improved with a boric ointment prescribed by Dr. Markus (acid. boric., 0.2; paraff. lig., 3.0; Vasel. ad 10.0). According to the patient this eye trouble is intermittent, occurring in attacks to which she has been subject for the last 4 or 5 years, a single attack lasting from one half to fourteen days, both eyes being usually affected at the same time, the right always worse than the left. The attacks are accompanied by dullness of vision (as explained by Dr. Markus), and usually (mostly in the right eye only) by a sensation of pricking, as if there were gritty particles in the eye.

The patient has been subject to Raynaud-like blueness of the hands and feet, which first occurred in a mild form after scarlatina at the age of 14 years. The blueness disappears when the patient is kept warm in bed.

For some years she has had a tendency to cough, doubtless owing to dryness of the mouth and pharynx. Tonsils removed as a child and again 8 years ago. All the teeth removed about 8 years ago. Appendix removed 14 years ago. Had pneumonia about 14 years ago. Superficial thrombophlebitis in the right leg about 4 years ago. Something like erythema nodosum in the left leg about 2 years ago.

The patient has moderate telangiectasia of the Osler type on the mucous surface of the lips and on the tips of the fingers. This

has been observed during the last 3 to 5 years. One of the telangiectases on the lower lip occasionally bleeds. She has never had epistaxis. There is no family history of telangiectasia. Other findings in the patient :—

Blood-count (July 4, 1936): haemoglobin 64 per cent.; erythrocytes 3,880,000; colour index 0.82; leucocytes 5,700 (eosinophils 3 per cent.; polymorphonuclear neutrophils 56 per cent.; lymphocytes 24 per cent.; plasma-cells 4 per cent.; monocytes 13 per cent.); thrombocytes 140,000. Fractional examination of the gastric contents (July 6) showed complete absence of free hydrochloric acid, even after subcutaneous injection of histamin; pepsin present only after histamin. Blood sedimentation-rate, greatly accelerated whenever taken; on January 23, 1937, it was 18 minutes (normal is over an hour by the method employed). The brachial blood-pressure is always very low; on January 23 it was 78/45 mm. Hg. A radiogram of the suprarenal region shows no calcareous shadows. There is no special cutaneous pigmentation. The blood-sugar is very low, but the fasting blood-sugar and blood-sugar curve could not be taken in the proper way. The urine, of low specific gravity, contains no abnormal constituents. The blood-serum gives negative Wassermann and Meinicke reactions. Blood-serum calcium (July 8, 1936): 8 mg. per cent. A radiogram of the skull shows a normal-looking pituitary fossa and a very thick calvarium. No abnormal shadowing in radiogram of the parotid glands. A radiogram of the thorax shows some excess of hilus shadowing on both sides. Menstruation has always been irregular; there has never been a prolonged period of amenorrhoea. I lost sight of the patient some years ago.

Chronic enlargement of parotid glands with recurrent exacerbations and moderate xerostomia.—This case was demonstrated by me at the Clinical Section of the Royal Society of Medicine on February 10, 1933 (Weber, 1933). The patient is a young married woman, aged 25 years. Married three and a half years. Has one child, aged 2½ years. Complains of intermittent swelling of the left parotid gland during the last ten years, and also of the right parotid gland during the last year. For the last three or four months the swelling has not completely disappeared on either side between the attacks. At present both parotid glands are definitely enlarged, chiefly the left one. There is often a little dull pain (not increased by pressure) over the parotid glands, especially on the left side. There has been moderate xerostomia during the last three or four months. The patient has noticed some viscid, tasteless material in the mouth at times, apparently secretion coming from the orifice of Steno's duct. Otherwise she seems to enjoy good health. Ordinary general examination, blood-count and urine show nothing special; menstruation regular. The blood-serum gives negative Wassermann and Meinicke reactions. No

obvious enlargement of the tonsils, lymph-glands, thyroid gland, spleen or liver. No kerato-conjunctivitis sicca or enlargement of the lacrimal glands. By radiographic examination of the parotid region and of the thorax, Dr. E. J. H. Roth finds calcification in the lymphatic glands draining the left parotid region, and there are discrete calcifications at the root of the right lung.

The exacerbations of the parotid swellings are not connected with meals; they seem sometimes to occur when she is not feeling well, especially in damp weather, but are not really seasonal and are not decidedly connected with the menstrual periods. The duration of the attacks has varied between three days and two weeks. (The swellings, as stated above, no longer quite disappear between attacks.) The patient has no artificial teeth and therefore the condition cannot in this case be connected with a badly-fitting (hard rubber) upper plate, and there is no pyorrhoea alveolaris.

I lost sight of the patient in 1933, but I mention the case here as typical of possible examples of "incomplete" Sjögren's syndrome.

Sjögren's syndrome associated with pigmentation and scleroderma of the legs, in a woman aged 43 years (Sheldon, 1938).—The illness commencing after the birth of her youngest child (8 years ago), has been slowly progressive. Dryness of the mouth (xerostomia), pharynx, larynx, nose (atrophic rhinitis with crusting and ozaena), and conjunctivæ; chronic fibrotic thickening (biopsy finding) of the submaxillary and parotid salivary glands (lacrimal glands not palpable); delusional mental changes; occasional epileptic fits; telangiectatic, pigmentary and scleroderma-like changes in the legs; no gastric achlorhydria found.

Dr. William Gilfillan (1939), of Adelaide, Australia, kindly wrote to me about a woman under his observation with Sjögren's syndrome and pigmentary changes in the legs similar to Sheldon's case. Under treatment with 1600 units of Vitamin A daily for 3 months, there was some improvement, in so far that the tongue, which had been red, glazed, fissured and very sore, became of normal colour, moist, with all the fissures healed. She could eat many things which for the last 15 years had been impossible. The salivary secretion, however, was not restored.

Sjögren's syndrome with widespread features including dryness and atrophic change in the vagina and almost complete alopecia.—In 1942 my colleague, Dr. H. K. Lauber, kindly showed me a woman, aged 48 years, with features of Sjögren's syndrome of 8 years duration. She had been seen by other doctors, and Dr. Herbert Levy, in particular, gave Dr. Lauber valuable information. In addition to the eye signs she had dryness of the mouth and to some extent of the nasal mucosa, and slight dysphagia, probably of the nature of a Plummer-Vinson syndrome and connected with pharyngeal (and oesophageal?)

dryness. There had also been considerable dryness of the skin. A striking feature was dryness with an atrophic change in the vagina. The parotid and submaxillary salivary glands and the lacrimal glands could not be palpated. During the last 4 years she had developed almost complete alopecia and had to wear a wig. No treatment had been successful. In regard to Plummer-Vinson syndrome in patients with Sjögren's syndrome see Franceschetti's paper (1942).

Sjögren's syndrome in which definite ocular changes were preceded by the salivary gland symptoms.—In March, 1944, with Dr. Kenneth Harris and Dr. B. Rogal, I saw a lady, aged 36 years, who had suffered from occasional swelling of the parotid and submaxillary salivary glands accompanied by dryness of the mouth and by a feeling of irritation in the eyes. She also complained of frequent dryness of the skin. I thought that the case might be one of commencing Sjögren's' syndrome and later on Mr. R. Lindsay Rea informed me that in October, 1944, he found keratitis in her left eye with reduced vision. This case is of interest because obvious ocular changes were preceded by the salivary gland symptoms.

Sjögren's syndrome: Possible association with Plummer-Vinson dysphagia and riboflavin avitaminosis.—Franceschetti (1942) found normal vitamin A values in patients with Sjögren's syndrome. In view of the frequency of joint symptoms and increased blood sedimentation-rate he did not think that an infectious factor could be excluded in the aetiology. He suggests that if the Plummer-Vinson dysphagia may be due to riboflavin deficiency, this deficiency may likewise be thought of as a possible cause of Sjögren's syndrome. It is interesting that he detected a porphyrinuria in two patients with Sjögren's syndrome. Owing to the observations of Franceschetti and others the benefit hoped for from vitamin A in Sjögren's syndrome (Stahel, 1938) cannot be regarded as realised. As previously mentioned, it seems to me that dysphagia of the Plummer-Vinson type may be directly due to local mucosal changes in Sjögren's syndrome.

Through Dr. Lauber I have heard of a case of dry mouth (? probably of the nature of Sjögren's syndrome) associated with "Adie's syndrome" (including non-tabetic and non-syphilitic absence of tendon reflexes), but I do not know the reference.

In the remarkable case of a woman, aged 26 years, in the discussion on which I took part (Lawrence, 1940), a chronic symmetrical atrophic sclerosis of the parotid salivary glands (perhaps of the nature of Sjögren's syndrome) was associated with so-called *lypodystrophia progressiva superior* and diabetic xanthoma. But the microscopical biopsy on one of the parotid glands showed the presence of true lymphatic follicles, as in "lymphadenoid" goitre, suggesting that the parotid condition was of the nature of an atrophic Mikulicz's disease.

Differential diagnosis

Apart from special ophthalmological features the following points have to be considered.

(1) Xerosis and ocular symptoms due to *deficiency of vitamin A* hardly enter into the question of diagnosis in England and treatment by vitamin A does not cure the cases under consideration (see above), even if it occasionally causes amelioration of some symptoms.

(2) There exist cases of *xerostomia of moderate degree of nervous origin*, which are not extremely rare and are not likely to be confused with the cases under consideration, though they too, I think, occur especially in women. There is also a kind of xerostomia of elderly persons (also mostly women), which may be partly due to senile atrophic changes in the salivary glands. There is also xerostomia due to chronic intake of toxic substances (see further on).

(3) *Mumps* should be mentioned here merely because most patients with recurrent parotid swelling have at first been suspected of having mumps. Rommel, however (quoted by Steinitz, 1929), mentioned a boy, aged 11 years, who had suffered five times from true epidemic parotitis.

(4) Cases of *recurring swelling of a salivary gland with meals*, due to obstruction in the duct, by a small calculus or foreign body do not need discussion here.

(5) I now come to a large chronic inflammatory group, the individual examples of which are obviously not all of the same nature, though for convenience I group them together here. The records, though scattered, are far too numerous to be mentioned here. A good deal of the literature is referred to by the authors I shall quote. *Some of the cases described by these authors might possibly be regarded, it must be admitted, as incomplete examples of Sjögren's syndrome* (compare some of Pyrah's cases, 1933).

- Cases of obstruction of the ducts by plugs of the type of Kussmaul's "sialodochitis fibrinosa" (1879), which in some cases affects both parotids, are relieved by the extrusion of the plug; this is followed by a flow of saliva and subsidence of the glandular swelling. The bilateral examples remind one of the rare cases of fibrinous bronchitis, possibly allergic in origin. Pearson (1936) reported two cases of recurrent swelling of the parotid glands due to obstruction of the ducts by plugs of mucus. In certain cases badly fitting dentures of hard rubber seem to have been a cause.

It should be noted that in the series of cases of chronic recurrent inflammatory parotid swelling recorded by Payne (1933) no striking degree of xerostomia nor any kerato-conjunctivitis sicca was observed, but 16 out of the 19 patients were women, reminding one of the proportion in Sjögren's syndrome. However, in

Pearson's somewhat similar cases in children (1935) the female sex was not affected more than the male. Pearson suggested that duct obstruction played a certain part, but that the infection in some cases might be superimposed on an allergic basis. Brown and Nevius (1936) described the case of a boy, aged 5 years, in whom the attacks ceased after removal of the tonsils and adenoids. Steinitz (1929) gives references to various cases of recurrent parotid swelling in children, not due to mumps.

Burton-Fanning (1925) recorded bilateral recurrent parotid swelling in a man, aged 62 years, apparently of allergic origin. Sir H. D. Rolleston suggested the term "asthma of Steno's duct" to describe the condition. In passing I would note that in idiosyncratic individuals bilateral swelling of parotid or submaxillary glands is an occasional manifestation of iodism (Weber, 1923). This may be connected with the excretion of iodide by these glands. (Lead also rarely causes parotid swelling.) The case of Londe and Pelz (1933) was a chronic one in a child with recurrent subacute exacerbations, benefited by intramuscular milk-injections. Meyer's patient (1934) with recurrent enlargement of salivary glands was a boy, aged 6 years, whose mother had been subject to similar attacks for the past twenty years, and whose maternal grandmother had suffered in the same way. The boy's attacks ceased when certain (presumably) offending foods were removed from the diet. In regard to this familial predisposition a case described by Remouchamps (1906) may be recalled. It was that of a man, aged 80 years, who had had bilateral chronic inflammatory swelling of both parotids from the age of 6 years, whose father was said to have suffered in the same way.

(6) It seems probable (as mentioned above) that in some of the Sjögren cases obstruction of ducts may play a causal part in the recurrent swellings of salivary glands, though not the primary cause of the syndrome. It seems also quite possible that there are cases in which the typical chronic inflammatory changes in the salivary glands lead to enlargement, sclerosis and atrophy without recurrent swellings. Such cases might clinically be confused with "incomplete" *Mikulicz's syndrome*, using the term to designate bilateral chronic progressive non-febrile and painless enlargements of salivary glands, especially the parotids, whether due to aleukaemic or leukaemic lymphadenosis or even myelosis, Hodgkin's disease, tertiary syphilis, tuberculosis, or (most important of all) lymphoid hyperplasia, the latter including the "true" cases of Mikulicz's disease. I admit of course that this inclusive use of the term Mikulicz's syndrome is not that of the writings of Mikulicz himself. According to Smith and Bump (1928) Mikulicz's disease proper is a lymphoid hyperplasia of the lacrimal and salivary glands with secondary destruction of the glandular parenchyma. They write that it is probable that the lymphoid

tissue, for the most part solitary nodes in and about the walls of the ducts, undergoes, or is subject to, diseases quite like those of lymphoid tissue elsewhere in the body. This makes me think of the striking lymphatic follicles in some cases of appendicitis. It seems to me that the lymphoid hyperplasia in Mikulicz's disease (according to the above definition) is probably analogous to the lymphoid hyperplasia (with true germinal centres of Flemming) in the thyroid gland seen in cases of lymphadenoid goitre. I am convinced that in cases of lymphoid hyperplasia of the parotid glands (incomplete Mikulicz's disease) there may sometimes be cystic swelling owing to duct-obstruction.

In the case of a woman, aged 61 years, shown by Critchley and Meadows (1932), with xerostomia and dryness of the eyes, a "biopsy" examination showed small round cell infiltration of a parotid gland, but there was no history of obvious swelling of any of the salivary glands and the total leucocyte count was 3000 per c.mm. of blood, of which 82 per cent. were lymphocytes. At first sight one might have thought of the possibility of an aleukaemic lymphadenosis; there was certainly hypogranulocytosis. But I suspect that the case was really one of Sjögren's syndrome.

(7) Finally, *Heerfordt's uveo-parotid syndrome*—more likely a form of sarcoidosis than "uveo-parotid tuberculosis"—has to be considered, for, surely, if a patient with Sjögren's syndrome were likewise for any reason to develop an attack of irido-cyclitis the case would probably be labelled Heerfordt's syndrome. To illustrate this difficulty I shall quote from Garland and Thompson's (1933) classical paper on "Uveo-Parotid Tuberculosis." On p. 164 these authors describe the following case as a not typical example, of Heerfordt's syndrome, but, having seen the patient myself and knowing more about the further history, *I now regard it as an example of Sjögren's syndrome in which secondary suppuration in salivary glands ultimately occurred:—*

"A woman, aged 55 years, was seen by Dr. Batty Shaw in January, 1928, when she complained of cough and loss of weight. Twenty years before she had complained of eye trouble, which had been diagnosed as irido-cyclitis, and which had relapsed in 1926, when a diagnosis of irido-cyclitis was again made by Dr. Griffith Thomas of Swansea. In addition to photophobia she now complained of dryness of the mouth, which has persisted. The recurrence of 1926 was also associated with painless swellings in front of both ears, but there was no pyrexia. At the time of examination in 1928 the only abnormality discovered was xerostomia. In September, 1930, she was seen by Dr. Macdonald Critchley; there was no family history of tuberculosis; on examination the pupils were unequal and inactive, the left cornea was hazy, the iris muddy, and the pupil irregular, the disc not being

seen. The right optic disc was normal. There was a flat swelling, painless, hard, and smooth, in front of the right ear; the left parotid showed diffuse, brawny, hard swelling. The other salivary glands, the lacrimal glands, and the lymph nodes were normal (that is to say, by naked eye examination and palpation—F. P. W.). The tongue was red, shiny, and dry, and there was marked xerostomia. Examination of the nervous system showed no abnormality (with the exception of bilateral ptosis); blood-pressure normal. X-ray examination of the chest showed no abnormality; blood-Wassermann reaction negative; blood-count normal; fractional test meal showed hypochlorhydria."

I can confirm all this personally, for the patient in question was sent to me in 1930 by Dr. Peter Milligan, then at Swansea, and I had the advantage of reports from Dr. Milligan and Dr. F. G. Thomas and Dr. H. R. Tighe, all of whom knew a great deal about her. I examined her thoroughly, partly at the German Hospital, and would only add that there was slight anaemia (with slight eosinophilia) then: Haemoglobin 61 per cent.; erythrocytes 3,120,000; leucocytes 4,000 (eosinophils 6 per cent.; polymorphonuclear neutrophils 72 per cent.; lymphocytes 15 per cent.; monocytes 7 per cent.). I might also mention that an acute suppurative parotitis on the left side had been incised and drained in August, 1930, and that later on the patient wrote to me that an abscess had been opened on the right side of her face on October 17, 1930. Dr. F. G. Thomas kindly informed me that the patient died in January, 1933, from broncho-pneumonia after a severe attack of influenza. The diagnosis in this case was never really settled (Weber and Schlüter, 1937) but I now regard it as a genuine example of Sjögren's syndrome, with secondary suppuration in salivary glands due to counter-infection—in spite of the history of irido-cyclitis.

Summary and conclusions

In this paper I have endeavoured to show of what great value Sjögren's ophthalmological writing is also for departments of medicine not specially connected with the eyes. I hope that increased knowledge of the syndrome and associated conditions will ultimately lead to the discovery of preventive measures against an insidious chronic and severe complaint which should be better known in general medicine. I shall not refer here to local palliative treatment of the kerato-conjunctivitis sicca, the xerostomia, etc.

Sjögren's syndrome forms one of a group of syndromes or diseases specially affecting the female sex, including exophthalmic goitre, lymphadenoid goitre, so-called lipodystrophia progressive superior, "idiopathic" hypochromic microcytic, and simple

achlorhydric anaemias, and perhaps ulcerative colitis. I need not allude to certain conditions connected with the pituitary gland, including Simmond's pituitary cachexia—nor to what has been termed its "functional counter-part," anorexia nervosa. According to C. A. Joll (1932) there are nine women for one man suffering from *exophthalmic goitre* in this country, though in Continental countries the proportion of men is higher; the greatest age incidence is in the third decade. Though *lymphadenoid goitre* is very little known on the Continent, Mr. Joll has met with quite a number of cases in this country. He finds that the sex preponderance is approximately six women to one man, and that the greatest age incidence is in the fifth and sixth decades. In regard to lymphadenoid goitre it is interesting that lymphoid replacement of glandular parenchyma is also a striking histological feature in some cases of chronic enlargement of salivary glands—that is to say, in the so-called "true" cases of Mikulicz's disease (see above).

Though the aetiology of Sjögren's syndrome—one might term it "Sjögren's disease," if we include the non-ocular features in the cases to which I have referred—has not been discovered, it appears not to be an avitaminosis, but to be of chronic inflammatory nature (witness the accelerated blood-sedimentation and the occasional arthritic complications) and mainly to affect females, usually at or past the climacteric period. Its manifold and generalised manifestations—especially in regard to the saliva, tear and sweat producing glands and the glands of the gastro-intestinal canal—can, I think, only be explained by some derangement of the vegetative nervous system, sometimes perhaps connected with structural or functional changes in the female sexual system. There may be a neuropathic predisposition.

REFERENCES

- BROWN, C. R. and NEVIUS, W. B. (1936).—*Amer. Jl. Dis. Child.*, Vol. LII, p. 1424.
- BURTON-FANNING, F. W. (1925).—*Brit. Med. Jl.*, Vol. II, p. 517.
- CAHANE, M. and F. (1930).—*Rev. franç. d'endocrinologie*, Vol. VIII, pp. 398-406.
- CRITCHLEY, M. and MEADOWS, S. P. (1932-1933).—*Proc. Roy. Soc. Med.*, Vol. XXVI, p. 308.
- DALSGAARD-NEILSON, E. and T. (1937).—*Ugeskr. for Laeg.*, Vol. XCIX, pp. 219-225.
- DUKE-ELDER, SIR S. (1930).—*Brit. Jl. Ophthal.*, Vol. XIV, pp. 61-65.
- FLAUM, E. (1932-1933).—*Wiener Arch. f. inn. Med.*, Vol. XXII, p. 201.
- FRANCESCHETTI, A. (1942).—*Confinia neurologia*, Basel, Vol. IV, pp. 309-368; Abstract in *Jl. Amer. Med. Assoc.*, 1943, Vol. CXXII, p. 713.
- GARLAND, H. G. and THOMPSON, J. G. (1933).—*Quart. Jl. Med.*, new series, Vol. II, pp. 157-177.
- GILFILLAN, W. (1939).—Private communication.
- GROSZ, ST. VON (1936).—*Klin. Monatsbl. f. Augenheilk.*, Vol. XCVII, pp. 472-485.
- HADDEN, W. B. (1888).—*Trans. Clin. Soc. Lond.*, Vol. XXI, p. 176.
- HUTCHINSON, J. (1888).—*Trans. Clin. Soc. Lond.*, Vol. XXI, p. 180.
- JOLL, C. A. (1932).—*Diseases of the Thyroid Gland*, London, pp. 360-361; also private information.
- KUSSMAUL, A. (1879).—*Berl. Klin. Wochenschr.*, Vol. XVI, p. 209.
- LAWRENCE, R. D. (1940).—*Proc. Roy. Soc. Med.*, Vol. XXXIII, p. 329.

- LONDE, S. and PELZ, M. D. (1933).—*Jl. of Pediatrics*, Vol. II, p. 594.
 MEYER, H. S. (1934).—*Jl. of Pediatrics*, Vol. IV, p. 248.
 PAYNE, R. T. (1933).—*Lancet*, Vol. I, p. 3-18.
 PAYNE, R. T. (1936).—*Lancet*, Vol. I, p. 655.
 PEARSON, R. S. B. (1935).—*Arch. Dis. Children*, Vol. X, p. 363.
 PEARSON, R. S. B. (1936).—*Guy's Hosp. Reports*, Vol. LXXXVI, p. 333.
 PYRAH, L. N. (1933).—*Brit. Jl. Surg.*, Vol. XX, p. 508.
 REMOUCHAMPS, E. (1906).—*Semaine médicale*, Paris, Vol. XXVI, p. 49.
 SHELDON, J. H. (1938-1939).—*Proc. Roy. Soc. Med.*, Vol. XXXII, p. 255.
 SJÖGREN, H. (1933).—*Acta Ophthal.*, Supp. II, pp. 1-151.
 SJÖGREN, H. (1935).—*Acta Ophthal.*, Vol. XIII, pp. 1-45. The latter reference includes a separate paper (pp. 40-45) on the histological changes in the nasal glands in cases of kerato-conjunctivitis sicca.
 SJÖGREN, H. (1938).—*Acta Ophthal.*, Vol. XVI, pp. 70-88.
 SJÖGREN, H.—*A new conception of Kerato-conjunctivitis Sicca*. (Keratitis Filiformis in Hypofunction of the Lacrimal Glands). English translation from the monograph published in Sweden in 1933, by J. Bruce Hamilton, Australasian Publishing Co., Sydney, 1943.
 SMITH, J. E. and BUMP, W. S. (1928).—*Annals of Surgery*, Vol. LXXXVIII, p. 91.
 STAHEL, W. (1938).—*Klin. Wochenschrift.*, Vol. XVII, p. 1692, and *Helvetica Medica Acta*, Vol. V, p. 579.
 STEINITZ, F. (1929).—*Monatsschr. f. Kinderheilk.*, Vol. XLII, p. 432.
 WEBER, F. P. (1923).—*Brit. Jl. Derm. and Syph.*, Vol. XXXV, pp. 169-180.
 WEBER, F. P. (1933).—*Proc. Roy. Soc. Med.*, Vol. XXVI, p. 526.
 WEBER, F. P. (1940).—*Proc. Roy. Soc. Med.*, Vol. XXXIII, p. 329 (remarks).
 WEBER, F. P. and SCHLÜTER, A. (1937).—*Deutsch. Arch. Klin. Med.*, Vol. CLXXX, pp. 333-340.

THE TREATMENT OF SEPTIC ULCER OF THE CORNEA BY LOCAL APPLICATIONS OF PENICILLIN*

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REPORTS from various sources have shown that the therapeutic results of penicillin applications to the eye are beneficial and occasionally dramatic.

Examples are to be found in the papers on catarrhal ophthalmias (Milner, Casiell, Crawford and King), ophthalmia neonatorum (Sorsby and Hoffa) and in deep infections (Rycroft).

Septic ulcer of the cornea with or without hypopyon is a matter of considerable clinical severity, and it is a fact well known to ophthalmologists of experience, that the prognosis with regard to the immediate cessation of the ulcerative process is a matter depending not only upon the virulence of the infecting organism, but also in a marked degree upon the general condition of the patient. The prognosis varies definitely with the age of the patient. In children ulcer with hypopyon responds well to ordinary routine treatment; but in old broken-down persons the prognosis may be bad indeed.

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