SJÖGREN'S SYNDROME TREATED WITH ACTH*

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IN this paper we report observations on the treatment with ACTH of six female patients suffering from Sjögren's syndrome. Each case was investigated on two occasions, an initial period of observation preceding the second admission for treatment. Five of the six patients underwent parotid biopsy, typical histological changes being seen in all. The methods used to assess improvement during therapy are described below.

Methods of Investigation

(1) **Schirmer's Test.**—Impairment of lacrimation with consequent dryness of the conjunctival sac may be estimated by inserting a strip of Whatman No. 41 filter paper, 5 mm. wide, over the lower lid into the conjunctival fornix. Normal subjects moisten from 10 to 20 mm./5 min. whereas those with kerato-conjunctivitis sicca give readings often as low as 1 or 2 mm. (Schirmer, 1903; de Rötth, 1941).

Schirmer's test was carried out at frequent intervals before, during, and after therapy. The results are summarized in Table I.

TABLE I
EFFECT OF ACTH ON LACRIMATION

Case No.	Age (yrs)	Ocular Symptoms		Total ACTH (g.)	Duration of Treatment (days)	Schirmer's Test (average mm.)		
		Duration (yrs)	Severity (0 to + + + +)			Before ACTH	During ACTH	After ACTH
1	52	3	+++	1	14	4.2	4.5	3.5
2	59	4	+++	1	10	4.0	4.0	4.7
3	36	2	+++	1	14	5.7	6.0	6.0
4	54	1	++	2.4	35	6.2	3.0	3.7
5	58	0.5	+	1	16	10.0	10.0	10.0
6	47	4	++	1	14	6.0	4.2	3.5
Mean and Standard Deviation						5.97±2.6	4.8±2.5	4.94±2.7

Statistical significance:
Columns 1 and 2 (before and during ACTH) $n=63$; $t=1.7059$; $P=0.05$
Columns 2 and 3 (during and after ACTH) $n=63$; $t=0.0976$; $P>0.9$
The decrease in lacrimation during treatment is just significant ($P=0.05$), but the experimental error renders such a degree of significance doubtful.

(2) **Slit-Lamp Examination.**—In Sjögren's syndrome 1 per cent. Bengal rose eyedrops stain the exposed or palpebral conjunctiva a bright red, two coloured triangles spreading from the limbus.

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The instillation of fluorescein at the same time enables slit-lamp demonstration of the characteristic filamentary keratitis, showing minute strands of eroded epithelium to which mucus and leucocytes adhere. The cornea also appears pitted and has small foci of degeneration in its deeper layers.

(3) Pilocarpine Salivation Test.—All saliva was collected in a dish for 30 min. after the injection of 11mg. pilocarpine nitrate subcutaneously. The normal range lies between 30 and 75 ml. of watery saliva, most of which is secreted by the parotid glands. According to Stones (1951) the maximum salivary flow may be as high as 190 ml. per hour. In cases with advanced parotid atrophy there is little response to pilocarpine and only a few millilitres of viscid mucus are obtained, the exact measurement of which is difficult because of froth.

(4) Ketosteroid Studies.—A preliminary investigation carried out by one of us (M.H.P.) assessed the total neutral 17-ketosteroids in the urine of ten female patients with Sjögren's syndrome. In three the quantitative composition of the steroids was measured by separation into eight main fractions by adsorption chromatography (Pond, 1951). The changes in 17-ketosteroid excretion after ACTH therapy was studied in three of the present series of patients.

(5) Clinical Observation.—Since all but one of our patients had been admitted previously and had subsequently attended the Clinic on many occasions, the natural history of the disease was already known. Subjective changes were noted and at the same time alterations in the size of the parotid swellings and changes in the joints and range of movement were recorded (Table II).

From previous experience it was realised that subjective improvement might occur with symptomatic treatment alone.

Case Histories

Case 1, Married female, aged 52 years.—Her eyes became sore and gritty 3 years before admission and she had no tears when she cried. Later that year her mouth felt dry, and she had superficial buccal ulcers and shortly afterwards recurrent parotid swellings. She also had rheumatic pains in the joints without swelling or limitation of movement, and nasal and vaginal irritation for a few months. When admitted the parotid glands were slightly swollen, the mouth was dry, and the tongue red. Slit-lamp examination of the eyes showed a well-developed filamentary keratitis and both lacrimation and salivation were much impaired. The sialogram showed widespread terminal duct dilatation. Total 17-ketosteroids 2.0 mg./24 hrs.

Treatment with 1 g. ACTH (Table II) at first reduced the ocular discomfort, but no significant degree of improvement resulted in any but the arthritic symptoms.

Case 2, married female, aged 59 years.—She developed a painless swelling of the left parotid gland accompanied by dryness of the mouth 5 years before admission, and at the same time noticed arthralgia in many joints without signs of frank arthritis. One year later the eyes began to irritate, she could not cry normally and there was a perpetual sticky discharge on the lids. She also had a recurrent purpuric skin rash and a dry cough. Examination revealed bilateral parotid gland enlargement, greatest on the left side, and a sialogram showed terminal duct dilatation. The mouth was dry and the tongue furred.

Thick ropy mucus was present on the cornea and conjunctiva, and slit-lamp examination showed a definite filamentary keratitis. There was no obvious arthritis. Total urinary 17-ketosteroids 2.6 mg./24 hrs.

A course of 1 g. ACTH relieved the eye symptoms but failed to increase lacrimation or salivation.

Case 3, married female, aged 36 years.—Rheumatoid arthritis, the initial disability, had developed 13 years before admission; 7 years later there was reactivity, and at the time of

TABLE II
EFFECT OF ACTH ON PAROTID GLAND FUNCTION AND SWELLING

Case	Xerostomia		Parotid Biopsy	Salivation after Pilocarpine (ml.) and Parotid Swelling (0 to + + + +)					
	Duration (yrs.)	Severity (0 to + + + +)		Before ACTH		During ACTH		After ACTH	
1	3	++	Left. Many areas of heavy lymphocytic infiltration with normal intervening parenchyma	10	+	9.8	+	8.2	++
2	4.5	+++	Left. Areas of granulation tissue heavily infiltrated by lymphocytes; normal parenchyma present	3.5	++	5.0	++	7.1	++
3	2	+++	Left. Some normal areas; in others dense lymphocytic infiltration with almost complete absence of acini	2.3	++	1.6	+	2.4	+++
4	1	+	Not done	13.7	0	9.3	0	11.5	0
5	0.5	±	Left. Infiltrated with lymphocytes, plasma cells, and fat, with relatively normal acini	21.3	±	22.3	±	19.7	±
6	2	+++	Right. Parenchyma much reduced, with many areas of dense lymphocytic infiltration	5.1	++	4.8	+	7.5	++
Mean and Standard Deviation				9.29 ± 7.3		8.57 ± 8.0		9.52 ± 5.8	

*Statistical significance:*Columns 1 and 2 (before and during ACTH) $n=32$; $t=0.2739$; $P=0.8$ Columns 2 and 3 (during and after ACTH) $n=32$; $t=0.3958$; $P=0.6$

There is no significant change in response during or after treatment.

admission she had widespread advanced joint deformities. Recurrent parotid swellings had first begun 6 years previously and for the past 2 years there had been permanent bilateral parotid enlargement most pronounced on the left side. Xerostomia was also troublesome. At the same time she also noticed a pricking sensation in the eyes accompanied by inflammation of the lids. Examination showed that the mouth was dry and the tongue red and sore. There was much ropy mucus in the eyes, and slit-lamp examination confirmed the presence of typical kerato-conjunctivitis sicca. A sialogram showed reduction in the number of peripheral branch ducts.

A course of 1 g. ACTH followed by 3.6 g. cortisone appreciably reduced the size of the parotid glands and improved the arthritis, though the latter returned with increased severity after cessation of treatment.

Case 4, married female, aged 54 years.—Rheumatoid arthritis had first developed 30 years ago and she still had pain and swelling of the finger and wrist joints together with

slight rheumatic activity in the knees and ankles. One year before admission her sight became blurred, the eyes felt perpetually sore, and xerostomia with recurrent superficial buccal ulcers developed. There was no parotid enlargement. Examination of the eyes showed an excess of mucus and the slit-lamp demonstrated a moderately well-developed filamentary keratitis. A sialogram was normal. Total 17-ketosteroids 1.2 mg./24 hrs.

2.4 g. ACTH given over a period of one month ameliorated the joint symptoms but produced little improvement in either ocular or buccal symptoms.

Case 5, married female, aged 59 yrs.—The initial disorder was rheumatoid arthritis which had persisted for 6 years with moderate activity; 5 years later she developed splenomegaly and leucopenia such as occurs in Felty's syndrome, the relation of which with the condition under discussion has been treated by one of us elsewhere (Gurling, 1953). Some time later she noticed slight dryness of the mouth, superficial ulceration, and mild irritation of the eyes. The parotid glands had never swollen noticeably, but the tongue was dry and glazed, the response to pilocarpine reduced, and the left parotid gland slightly enlarged. The eyes appeared normal, but slit-lamp examination revealed definite signs of kerato-conjunctivitis sicca. A sialogram was normal. Total urinary 17-ketosteroids were 1 mg./24 hrs.

With 1 g. ACTH there was improvement in the arthritis but no significant benefit otherwise. The white cell count rose no higher than 3,000 per c.cm.

Case 6, married female, aged 47 years.—For 17 years she had been troubled by rheumatoid arthritis with long periods of remission, and 5 years before admission there had been generalized reactivity. The first parotid swelling developed 6 years before admission but subsided after a few weeks, xerostomia being noticed 2 years later. Subsequently she had persistent parotid swellings and acute staphylococcal abscesses on two occasions. Her eyes had also been "gritty" and the lids sticky for 4 years. When examined both parotid glands were swollen, the mouth dry, and the tongue furred. There were petechiae on the legs and feet. A left sialogram showed dilation of the main duct and the finer branches did not fill. The characteristic picture of kerato-conjunctivitis sicca was seen under the slit lamp.

The arthritis and ocular symptoms were temporarily relieved by 1 g. ACTH, though no objective changes were noted, except that the parotid swellings became smaller. Later, 3.2 g. cortisone given intramuscularly over a period of 3 months also controlled the parotid swellings to some degree but did not increase lacrimation or salivation.

Treatment and Progress

All six patients were given ACTH by intramuscular injection commencing with 25 mg. 6-hrly, reducing to 50 or 75 mg. a day in some cases, treatment being continued from 10 to 35 days.

Five received a total dose of 1 g. and the sixth 2.4 g., whilst three were subsequently given cortisone in doses of up to 150 mg. a day to a total of 3.5 g. Artificial tears and saliva stimulating lozenges were discontinued during treatment.

Effect on the Eyes.—All six patients complained of typical ocular symptoms for periods varying from 6 months to 4 years and the diagnosis of kerato-conjunctivitis sicca was confirmed by slit-lamp examination. In two cases these symptoms were less prominent than other non-ocular manifestations of the syndrome. Schirmer's test showed definite impairment of lacrimation in all except Case 5, in which the results were borderline, particularly for the left eye.

It will be seen that no significant improvement could be detected (Table I). Five patients obtained transient symptomatic relief, but there was no obvious change to be seen macroscopically and re-examination under the slit lamp failed to show any difference.

Effect on the Mouth and Salivary Glands.—Five of the six patients complained of dryness of the mouth of up to 3 years' duration, often fluctuating in severity and in no case sufficient to cause serious dysphagia. The sixth patient had never previously complained of xerostomia though her tongue was dry and the epithelium atrophic.

The response to pilocarpine is shown in Table II. The volume of saliva was less than 10 ml. in three cases, between 10 and 20 ml. in two, and up to 25 ml. in the sixth, readings which may be considered pathological in all but the last case. Treatment with ACTH and cortisone failed to bring about any greater improvement than might have occurred spontaneously, and in no case was the volume of saliva raised to normal. In Case 2 a result 17 days after treatment was double that obtained initially, though the figure was still pathologically low. A variation of a few ml. in either direction was common and often bore no relation to treatment. Parotid swellings were present at the time of admission in five patients. In Case 1 pus could be expressed from Stenson's duct and in Case 6 there was an abscess due to *Staph. aureus* infection. A parotid biopsy was carried out in five of the six cases before treatment was started and characteristic lymphoid infiltration was seen in each. Areas of apparently normal gland parenchyma were present in each case, and it is of interest that histological changes and parotid enlargement were least in Case 5, where the salivary gland function was almost normal.

A considerable reduction in the size of the swellings was observed in Case 3, and a lesser response in Case 6, but in both the effect was temporary only. In Cases 1, 2, and 5 swelling was minimal at the time of treatment and there was no appreciable alteration. Those patients with atrophy and redness of the tongue also failed to show the improvement that might be expected if there were any local effect on the mucosa or submucosal glands irrespective of alterations in salivary flow.

Effect on the Arthritis.—Rheumatoid arthritis had developed before the other symptoms in all four cases in which it was present. It was the usual type of atrophic arthritis, severe in Cases 3, 5, and 6, and mild in Case 4. Treatment with gold and physiotherapy had been given intermittently in all four. The two other patients, Cases 1 and 2, had no signs of arthritis, but both had suffered from variable joint pains of the type described as "arthralgie fugaces" by French physicians. The response to ACTH in the three cases with active arthritis was satisfactory, relief of pain and a clear improvement in range of movement being obtained. One patient had a severe relapse within a few days of stopping treatment and later failed to do well with cortisone. The patient with mild chronic arthritis (Case 4) was also partially relieved, and one of the two suffering only from arthralgia and soft tissue pains (Case 1) also stated that her symptoms were relieved.

The good effect of ACTH on the arthritic component of Sjögren's syndrome was not related to the degree of improvement in buccal and ocular disturbances.

Urinary 17-Ketosteroid Studies

The results of the total 17-ketosteroid studies have been reported more fully elsewhere (Pond, 1954) and are here given briefly. All estimations gave figures between 1 and 3 mg. 24 hrs, the average of 2.4 mg. being below the lower limit of normal in women (for this laboratory—4 to 14 mg.).

Fractionation failed to throw light on the reason for these low total values,

as each fraction was reduced in all patients, the β fraction most particularly, whilst the 11-oxy-17-ketosteroids, breakdown products of the adrenal corticoids, were within normal limits. One patient showed a relatively raised eticholanolone excretion, which other workers have suggested was characteristic of debilitating or malignant disease (Robinson and Goulden, 1949). The administration of ACTH resulted in a two- to six-fold increase in the total neutral 17-ketosteroid excretion in Cases 1, 3, and 4. This is in agreement with the findings in normal subjects of Forsham, Thorn, Prunty, and Hills (1948) and suggests potentially normal adrenal cortex function. It seems probable that the initially low figures reflect both the debilitating nature of the disease and the age of the patients rather than any fundamental endocrine abnormality. There was no obvious correlation between rise in 17-ketosteroid excretion and clinical improvement.

Discussion

In the six cases under review, treatment with ACTH led to no significant improvement in lacrimal or salivary gland function or to improvement in either kerato-conjunctivitis sicca or xerostomia. The repeated measurements of lacrimal and salivary gland secretions by means of Schirmer's test and pilocarpine stimulation as well as slit-lamp examination failed to reveal any objective therapeutic response. The slight symptomatic amelioration noticed by some patients was of short duration, varied in nature in each individual, and was no greater than we have observed during the natural course of the disease. In two cases, however, there was a definite reduction in size of the parotid glands, indicating the presence of some influence on the lymphoid infiltration which appears to cause swelling. This improvement was unaccompanied by any restoration of secretory function and is probably a non-specific ACTH effect. In all biopsy specimens some microscopically normal gland parenchyma was present, the amount of which was roughly in inverse proportion to the degree of parotid swelling and impairment of salivation, so that restoration of function appeared possible if in fact ACTH was of any use. In other cases not included in this study, more advanced histological changes were seen in the parotid gland tissue, amounting to complete destruction of the acini with replacement by adipose and fibrous tissue through which ran dilated ducts. In such cases no improvement in function could be expected, but no such advanced cases were treated.

All patients with arthritis or joint pains were relieved as in uncomplicated rheumatoid arthritis, suggesting that the arthritic lesions differ in aetiology from those in the parotid and lacrimal glands and other epithelial surfaces.

The significant increase in urinary 17-ketosteroid excretion, and the gain in weight and eosinopenia seen in most patients demonstrated that the ACTH used in this trial provided adequate adrenocortical stimulation. All patients have since been followed up for at least one year, but in none has the course of the syndrome undergone any significant modification. Our observations

are in agreement with those of Cadman and Robertson (1952), who found that ACTH reduced the size of parotid swellings so long as treatment was continued, but had no effect on buccal or ocular symptoms. We did not, however, observe any reduction in splenomegaly in Case 4, such as was noted in one of their patients. Fitzgerald and others (1951) doubted the value of ACTH, but Frenkel and others (1951) thought that both lacrimation and salivation were considerably increased for one month after treatment, and Stephens (1950) also considered his case temporarily improved.

Although ACTH and cortisone may be used in the treatment of the arthritic element with undoubted benefit, it seems to us that symptomatic treatment is more effective in the relief of other symptoms. Artificial tears or diathermy of the lacrimal puncta often relieve the ocular symptoms, and radiotherapy is of value in unsightly parotid swellings though all trace of function is destroyed. The 17-ketosteroid studies gave no evidence of basic endocrine abnormality in spite of low urinary values.

Summary

(1) Six cases of Sjögren's syndrome were treated with ACTH in amounts of 1 to 2.4 g.; three also had cortisone.

(2) In no case was there any appreciable increase in parotid or lacrimal secretions in spite of the presence of a proportion of normal acinar tissue in parotid biopsy specimens.

(3) Arthritic symptoms improved as in uncomplicated arthritis.

(4) From 17-ketosteroid excretion studies there was no clear evidence of an endocrine disorder in Sjögren's syndrome, and a rise in output following ACTH did not necessarily parallel clinical improvement.

(5) Neither ACTH nor cortisone seemed to be of greater value than symptomatic treatment.

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