Acta Medica Scandinavica. Vol. CXLIX, fasc. VI, 1954.

From the Medical Department of the »Onze Lieve Vrouwe Gasthuis», Amsterdam, Holland.

The Effect of Cortisone on Sjögren's Syndrome.

By

W. K. GAULHOFER.

(Submitted for publication February 25, 1954.)

In 1933 Sjögren (1) described a syndrome, comprising kerato-conjunctivitis sicca with diminished lacrimal secretion, rhinopharyngolaryngitis sicca with decreased nasal secretion, recurrent parotitis with diminished secretion of saliva and in some cases gastric achylia. Recent investigations, amongst others those of Holm (2) and Henderson (3) have shown that mild forms of this syndrome are relatively frequent, especially in combination with rheumatoid arthritis. This too was the author's experience in the examination of 456 cases of rheumatoid arthritis in the »Anti-Rheumatic Centre» in Amsterdam (director: Dr. J. v. Breemen), when symptoms of Sjögren's syndrome were found in 40 instances. It is therefore not surprising that various authors have tried to find whether the Sjögren syndrome, like rheumatoid arthritis, can be favourably influenced by ACTH or cortisone.

The results of this treatment are very divergent. Two authors record successes. Stephens (4) observed the development of a copious secretion of tears and saliva over an unspecified number of days after giving i.m. ACTH injections for 10 days to a 50-year-old woman suffering from Still's disease and Sjögren's syndrome.

Frenkel and co-workers (5) also observed a marked increase of lacrimal and salivary secretion during 4 weeks' treatment with ACTH in a 51-year-old woman with a severe non-rheumatic form of Sjögren's syndrome. Shortly after the suspension of ACTH-treatment the secretions dropped again to the original level. Neither of these authors reports about measurements of the volumes of the secretions.

No increase in the amount of secretion in Sjögren's syndrome, could, on the other hand be found by Fitzgerald and co-workers (6), Appelmans and co-workers (7), Cadman and Robertson (8) and Sjögren and Eriksen (9) with i.m. administra-

sone, by Cadman and Robertson, Coste (10), Offret (11) and Forestier (12) with intraconjunctival application of cortisone and by Duke-Elder (13) with subconjunctival injection of cortisone.

Some of these authors made measurements of the lacrimal secretion but did not measure the amount of salivation.

As we have developed a semi-quantitative technique for the measurement of the salivary secretion we have determined in 6 patients with Sjögren's syndrome the amount of salivation as well as of lacrimal secretion (and the acidity of the gastric juice) during and after treatment with cortisone (ACTH respectively).[1]

Methods.

Measurements of lacrimal secretion.

The amount of secretion was ascertained by the Schirmer test without previous anesthesia of the eye. Strips of pink litmus paper (Johnson's), 5 mm broad and bent 4 mm from the end, were hooked into the outer corner of the eye behind the lower lid and left there for 5 minutes. Three strips were used in every test but not as in the original method one immediately after the other but at intervals of about 9 minutes. This modification was necessary to permit simultaneous measurement of salivation. The amount of lacrimation was judged from the length of the litmus strip (excluding the folded edge) which had been turned blue by the tears.

In the following report only the mean of each set of 3 measurements is given. Wetting-lengths of 15 mm or more are generally considered normal; 5—14 mm suggests a slight and 0—4 mm a pronounced reduction of lacrimation.

Measurement of salivation.

Salivation was measured by the method described by the author in Ned. Tijdschr. v. Geneesk. (14).

Over a series of 15 (or less) consecutive periods of 3 minutes, one dragée and 2 dentist's cotton wool rolls are placed in the mouth each time — the rolls at the left and right under the tongue, the dragée on top of the tongue. The dragée must not be chewed or sucked. The rolls and the dragée are weighed before insertion and again after removal. Their increase in weight corresponds to the amount of saliva secreted during their presence in the mouth. Before insertion of the 4th pair of cotton wool rolls, 5 mg pilocarpine hydrochloride is injected subcutaneously as a stimulus to salivation. The results are recorded graphically.

Figure 1 shows a few examples. Curve VI is the highest of those found in 50 normal subjects. Curve IV is the lowest. Curve V shows the arithmetic mean of all 50 sets of results.

It can be shown from this that normal persons produce 3.4 ($\pm$ 1.3) g saliva

[1] All patients were treated in the »Onze Lieve Vrouwe Gasthuis» in Amsterdam by a team studying problems of cortisone-treatment financed by a grant from the »Netherlands National Health Council».

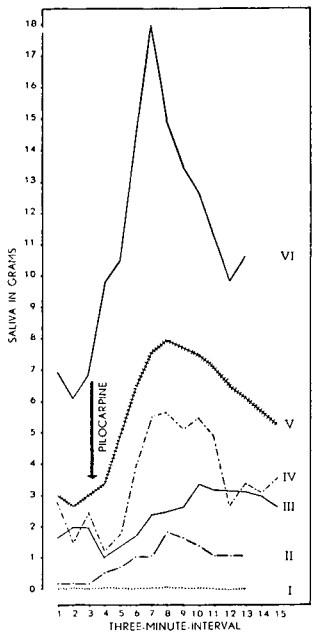

Fig. 1. Curves of salivary secretion. Curves I, II and III are from cases of Sjögren's syndrome. Curve I from a severe case complicated by parotitis. Curve II from a case of moderate severity. Curve III from a mild case of Sjögren's syndrome. Curve IV. The lowest curve found among 50 normal subjects. Curve V. Curve compiled from the arithmetic mean of 50 normal subjects. Curve VI. Highest curve obtained from 50 normal subjects. These curves indicate the secretion of saliva measured in grams during 13—15 3-minute periods before and after injection of 5 mg pilocarpine hydrochloride.

in 3 minutes if no strong stimulus is applied. After stimulation of salivation with pilocarpine a maximum of 7.8 ($\pm$ 2.6) g is secreted in 3 minutes.

Curves I—III are taken from patients with Sjögren's syndrome. Curves of type I are found only in the most severe forms of the disease, which are accompanied by parotitis. The curves do not begin above 0.05—0.2 g and do not show any elevation after injection of pilocarpine. Curves of type II are found in moderately severe forms of the disease. They start at a lower value than normal curves and do not rise as high as normal curves after injection of pilocarpine. Curves of type III show the slightest deviation from normal. They begin, in contradistinction to type II curves, at as high values as normal curves, only they do not rise as high as normal curves after injection of pilocarpine.

These curves are reproducible. If the test is repeated under the same conditions 1—7 days later the maximum values do not differ by more than 1 g from the value obtained the first time, provided this was not more than 9 g. In this case the difference in a subsequent test may be as much as 3 g.

Case Histories.

Case A: a 49-year-old housewife who had suffered from rheumatoid arthritis for 12 years and for the past 3 years had not been able to produce tears on crying. Her

lowered (1 mm left and right). Her salivation was slightly reduced (type III from fig. 1). Max. gastric acidity 55/72. Diagnosis: rheumatoid arthritis (stage II according to the classification of the New York Rheumatism Association) and a moderately severe form of Sjögren's syndrome.

The patient was treated for 76 days with cortisone and temporarily with Au or Irgapyrin (for dosage see fig. 2). Under this treatment there was a rapid improvement in the joint symptoms, which reached a maximum on the 16th day of treatment. After this the condition deteriorated, slowly at first, and then more rapidly and after the cessation of the cortisone treatment was worse than before the treatment was started.

As can be seen from figure 2 the lacrimal secretion was not improved by cortisone. Salivation, however, increased considerably and reached almost double the initial value, simultaneously with the maximal improvement in the rheumatic symptoms. Parallel with the ensuing deterioration of the articular symptoms, salivation decreased too and reached the initial level after treatment. The patient's gastric acidity did not alter during treatment.

Case B: 42-year-old teacher who had suffered from rheumatoid arthritis for 11 years. She could cry with tears and did not complain of a dry mouth. Her lacrimal secretion was slightly lowered (8 mm), salivation was slightly reduced (curve III, fig. 1). Her eyes did not stain with Bengal Rose. Gastric acidity max. 32/58. Diagnosis: rheumatoid arthritis (stage II) and a mild form of Sjögren's syndrome.

With low doses of cortisone (see fig. 3) an improved mobility of the joints first appeared on the 19th day of treatment. From the 49th to the 70th day of treatment the condition was fair. After this the joint complaints markedly increased. After the suspension of the cortisone medication a febrile exacerbation developed. Finally there was a certain improvement under subsequent treatment with ACTH and Irgapyrin.

Shortly after the initial improvement in the rheumatic symptoms, on the 21st day of treatment, the lacrimal secretion was found to have risen to a normal level. After the cessation of cortisone administration the lacrimal secretion fell to a very low level only to rise again with Irgapyrin and ACTH.

The secretion of saliva increased later however than the secretion of tears. In the pause in treatment between cortisone and ACTH salivation did not decrease. The gastric acidity was not checked in this patient.

Case C: 50-year-old housewife who had suffered from rheumatoid arthritis for 6 years. For the past 3 years when she cried only a few or no tears appeared. She did not complain of a dry mouth. On admission rheumatoid arthritis (stage II) was found, and a moderately severe form of Sjögren's syndrome (marked colouration of cornea and conjunctiva with Bengal Rose, markedly reduced lacrimation (2 mm) and a slight decrease in salivation (type III, fig. 1)).

A histamine-refractory gastric achylia was present.

Under treatment with cortisone (dosage see fig. 4) the mobility of the joints improved until the 34th day, whereafter it decreased again. After cortisone was discontinued there developed a febrile exacerbation with violent joint pains which persisted until treatment with ACTH was begun. With this a slight and transitory improvement in the joint symptoms was achieved.

From figure 4 it can be seen that the secretion of tears remained more or less unchanged throughout the entire treatment, whilst the secretion of saliva rose temporarily with cortisone as well as with ACTH. Increase in salivation coincided with the improvement in the articular symptoms, whilst the decrease in the secretion ran parallel with the deterioration of the joint symptoms.

The achylia remained histamine-refractory throughout the whole treatment.

arthritis stage III and a fairly severe form of Sjögren's syndrome were found (lacrimation 3 mm, salivation slightly decreased: type III, figure 1). Bengal Rose colouration negative.

During the treatment with cortisone (dosage see figure 5) a rapid improvement in the articular symptoms was reached, which improvement was entirely lost after the end of the treatment. The lacrimation once during the treatment showed a somewhat higher value than before or after treatment. The salivation on the 11th day of treatment, when the articular manifestations were clearly improved, was found to have risen to 7 g. Thereafter it fell to its initial level. On the 18th day of treatment pains began in the gastric region and the gastric acid values (45/22 before treatment) were found to have risen to 98/95. The gastric pains disappeared with antacids. This hyperacidity continued throughout the entire period of treatment.

Case E: 64-year-old housewife who had not been able to cry with tears for 4 years. For the same period there had been no secretion from the nose and she could no longer swallow dry food. Her tongue and lips burned when they came into contact with spiced or salty foods. On three occasions during the previous 2 years an inflammation of the right parotid gland had arisen. On examination, swelling of both parotids and the left submaxillary gland was found. The tongue was red and smooth. The lips displayed rhagades. Both conjunctivae and corneae coloured strongly with Bengal Rose. A rhinitis sicca was present. The secretion of tears was markedly reduced (2 mm). Salivation was more or less absent (type I from figure 1).

E. S. R. 41 mm. There were no abnormalities of the joints.

Under treatment with cocarboxylase (Berolase 'Roche') and vitamin B-complex i.v. and i.m. (Becozym 'Roche') the rhagades disappeared without any increase in secretion. We did not care to administer cortisone i.m. because of the chronic recurrent parotitis. In consultation with the ophthalmologist, Dr. Winkelman, and under his supervision, cortisone eyedrops (1 drop 3 times daily in the left eye) were given over a period of 6 weeks. From the first day of treatment the pain in both eyes was less. Lacrimation and salivation however, did not increase.

Case F: 43-year-old woman, who had suffered from parotitis 6 times in the past 5 years. She could no longer produce tears when she cried. On examination a marked Bengal Rose colouration of both eyes, a markedly decreased lacrimation (0 mm) and a markedly decreased salivation (type I from figure 1) were found.

In this patient too, general treatment with cortisone was not considered desirable and cortisone was applied locally as eye drops in the right eye, over a period of 24 days. Here too, the patient's ophthalmic complaints disappeared, whilst the secretion of saliva and tears remained unchanged.

Discussion.

Six cases of Sjögren's syndrome — 4 rheumatic and 2 non-rheumatic — were treated with cortisone (and ACTH).

In the two non-rheumatic cases (E and F), where Sjögren's syndrome was especially severe and associated with recurrent bacterial parotitis systemic treatment with cortisone was judged inadvisable in view of the danger of exacerbation of infection and the patients were treated with cortisone eye drops.

This did not lead to any significant increase in the secretion of tears. Both patients, however, were relieved of the disagreeable symptoms in both eyes during the period of treatment, although cortisone had been introduced into one eye only

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.