temporarily to an acute ward. Another aggressive young schizophrenic showed an increase in impulsive, mischievous, and aggressive conduct two weeks after starting the drug. This phase continued for three to four weeks, though the drug was stopped four days after the change began. A paranoid juvenile schizophrenic case, not particularly immature physically or emotionally, became more acute with increased tension, attempted to smash a window, and required heavy sedation to relieve the situation.

Discussion

The most significant effect of dehydro*iso*androsterone is that it modified the behaviour of selected juveniles, and this effect was consistent in trend and form. Those who were socially and emotionally inadequate gained by becoming more normally confident, alert, and able to mix with their fellows. Those liable to be over-aggressive in mental make-up were made worse and appeared overstimulated by the drug. In both types the effect was temporary, since the "inadequate" patients, with two exceptions, tended to relapse, and the aggressive settled down to their usual state when the drug was discontinued. The presence of schizoid, anxious, or depressed features seemed to be of secondary importance in the selection of patients for this treatment, provided the inadequacy was present, as just described. Pending further investigation it can be said that dehydro*iso*androsterone acts as a form of replacement therapy, and that effective treatment is likely to be prolonged and the dosage varied according to individual needs. The usual range lies between 5 and 30 mg. or more, whether by injection or in tablet form.

Total 17-ketosteroid estimations, with two tests per patient, were performed in all cases. Irrespective of clinical type, half the patients proved to be within the average range for their age group and half were found to have low ketosteroid output in the urine. Estimation of total 17-ketosteroids was of little value in the selection of patients for treatment, which was done entirely on clinical grounds, as described. There is some indication, as noted in the paper of Strauss *et al.*, that selection may be possible through the fractional estimation of the 17-ketosteroid group. No alteration in primary or secondary sexual characteristics was noted. Dosage should be related to individual needs, not only for adequate treatment but to avoid complications.

The electroencephalogram was recorded in all but one case. The number of normal results exceeded the usual proportion for this age range in those admitted to the juvenile unit. No significant deductions could be made in this small series.

All cases had failed to respond to other measures before dehydro*iso*androsterone was begun. In this group of thirteen inadequate cases two recovered during treatment, five were much improved, three improved, and three others showed only temporary gain. None were worse, as happened temporarily in the four aggressive cases. Eight patients have been discharged.

Follow-up for the maximum of a year after the drug was stopped showed that of the thirteen patients only three have continued in their recovered and improved state, while the rest have suffered varying degres of relapse. It is obvious that in many cases the treatment will require to be prolonged over months to be of any lasting value.

While this treatment may replace certain factors lacking for normal constitutional endowment, it is not a substitute for proper psychotherapeutic investigation, though progress in psychotherapy can be accelerated through improved rapport. Furthermore, the gain in self-confidence enables many of these cases to take up the ordinary social and occupational pursuits of adolescence.

We are most grateful to Dr. W. W. Kay and to Mr. L. D. G. Hamilton, of the Mental Hospitals Group Laboratory, West Park Hospital, for their assistance and advice on 17-ketosteroid estimations; also to Organon Laboratories for supplies of dehydro*iso*androsterone.

REFERENCE

Strauss, E. B., Sands, D. E., Robinson, A. M., Tindall, W. J., and Stevenson, W. A. H. (1952). *British Medical Journal*. 2. 64.

THE TREATMENT OF SJÖGREN'S SYNDROME WITH A.C.T.H.

BY

EWAN F. B. CADMAN, M.D., M.R.C.P., D.C.H.

AND

A. JOHN ROBERTSON, M.D., M.R.C.P.

(From the Department of Medicine, University of Liverpool)

In 1933 Sjögren described the ocular component of the condition which now bears his name, and which is becoming more widely recognized. It occurs mainly in middle-aged women, and consists of dry mucous membranes, parotid gland enlargement, and arthritis, though the syndrome is often incomplete. Kerato-conjunctivitis sicca is an essential part of the disease, and rhinitis sicca, xerostomia, pharyngitis sicca, and laryngitis sicca may occur. The lacrimal glands are involved but rarely palpable. In addition, an increased erythrocyte sedimentation rate, hypochromic anaemia, low blood sugar, achlorhydria, and alopecia have also been described (Weber, 1945).

A.C.T.H. has been used by us to treat two cases, and these are discussed below.

Case 1

A 60-year-old housewife was first seen in June, 1951, complaining of a dry mouth. Apart from some rheumatoid arthritis which began after the menopause at the age of 51, she had been perfectly well until March, 1948, when she had "influenza." She was kept in bed for a week with generalized aches and pains and loss of appetite, and immediately afterwards she noticed a wide variety of symptoms. Her sense of taste and smell disappeared, and her eyes became sticky and dry. Her mouth became very dry, making many foods difficult to chew, and she noticed that she was getting swellings near the angles of her jaw. These changed the shape of her face, seemed to vary a little in size, and were sometimes painful. Cracks developed at the corners of her mouth in June, 1950, but otherwise her symptoms had continued unchanged for about three years.

On examination each parotid gland was much enlarged but not tender, and she had severe rheumatoid arthritis with ulnar deviation in her hands. Her tongue was smooth, dry, and magenta-coloured, and her mouth was dry. There was an angular cheilosis, and she had kerato-conjunctivitis sicca. In addition there was a greatly enlarged liver and spleen, each being about five fingerbreadths below the costal margin.

A clinical diagnosis of Sjögren's syndrome was made, but the various laboratory investigations failed to reveal the underlying pathology or to account for the hepatic and splenic enlargements. Her plasma proteins were abnormal, in that she had a total of 9.2 g. per 100 ml., with albumin 3.55 g., globulin 5.65 g., and A/G ratio 0.63/1 by Howe's technique. Her gamma-globulin was 4 g. per 100 ml. (Cohn's technique), and no doubt this accounted for the abnormal flocculation tests, which were compatible with hepato-cellular damage. A liver puncture showed no abnormality of the liver cells, but one portal tract was filled with lymphocytes. The haemoglobin was 11 g. per 100 ml., with 3,700,000 red cells per c.mm. There was a neutropenia with a total of 2,000 white cells per c.mm. (280 polymorphs, 1,100 lymphocytes, 560 monocytes, 20 eosinophils, and 40 basophils). The sternal marrow was within normal limits, as were the blood-calcium, blood-phosphate, blood-sugar, urine, bleeding-time, clotting-time, and prothrombin-time estimations. The fractional test meal showed a low acid curve, and *x*-ray films of the hands and

shoulders showed typical changes of rheumatoid arthritis with some osteoporosis. Chest *x*-ray films and lipiodol bronchography revealed some left lower lobe bronchiectasis. The serum alkaline phosphatase was considerably raised at 75 units, and the E.S.R. was 29 mm. in one hour (Wintrobe).

Schirmer's filter-paper test showed moistening of the paper to 1.5 mm. in the left eye, and to 0 mm. in the right eye, as compared with a control of 20 mm., in three minutes, and the rose bengal test stained only the visible conjunctivae. No secretion could be obtained from either parotid gland, and a sialogram showed only very small intraglandular ducts.

In August, after a trial period on pilocarpine (with no change in salivation or sweating), she began treatment with a 100-mg. dose of A.C.T.H. daily by intramuscular injection. Within two weeks the parotid swellings had virtually disappeared, her liver and spleen were very much smaller, and her fingers were much freer. There was no improvement in salivation or in her eyes.

The A.C.T.H. was reduced gradually until she was getting 10 mg. once weekly and had had a total of about 4,000 mg. The treatment extended over six months, during which time her parotid glands, liver, and spleen, while varying a little from time to time, have remained more or less unchanged at their new small size, but there has been no improvement in the main symptom of a dry mouth. No substantial change was found on repeating the investigations, though the neutropenia has disappeared.

Case 2

A 54-year-old housewife was first seen in September, 1951, complaining of a dry mouth, sore eyes, and swellings at the angles of her jaw. She had been well until 1946, when she felt "run down"; a year later she was thought to be anaemic. In 1948 she was fitted with a complete set of dentures after the extraction of her last 10 teeth, and a few months later she noted that her mouth was dry, and that she had difficulty in chewing and swallowing solid foods. At about the same time her eyes became sore and she felt as if something was in them. A discharge would appear over the cornea, interfering with vision, and tears would not come even when she was crying or was peeling onions. Spectacles were prescribed without improvement.

In 1949 the parotid swellings were first noticed; there has been no fluctuation in their size since then, but occasionally they have been tender. Her condition continued unchanged until September, 1951, when she came into hospital, though she had been jaundiced for six weeks in 1950. She mentioned that her body hair had become scanty, and that she had sweated very little since the menopause in 1938.

On examination both parotid glands were enlarged and slightly tender; the orifices of Stenson's ducts on both sides were clearly visible. Some debris was present over the bulbar conjunctivae, and a little fluid was visible in the conjunctival recesses. There were rhagades around the mouth, and her tongue was dry and fissured. Heberden's nodes were present, but there was no other evidence of arthritis. Pubic and axillary hair was scanty, and the axillae were dry, but her palms and soles were moist. The rest of the examination was within normal limits, and a clinical diagnosis of Sjögren's syndrome was made.

Schirmer's filter-paper test showed moistening of the paper to only 3 mm., compared with a normal control of 40 mm., and the rose bengal test stained only the visible conjunctivae. Massage of the parotid glands produced at first a glairy mucoid fluid, and later a clear watery fluid with an amylase content of 9 units per ml. (normal 100–150 units per ml.). Although a slight increase in flow came after drinking lemonade, there was no response to pilocarpine or chewing paraffin wax, and iodide could not be found in the saliva after a dose of potassium iodide.

A liver puncture showed evidence of portal fibrosis, and the liver function flocculation tests were ++++, though the serum bilirubin and the serum alkaline phosphatase were normal. The peripheral blood picture showed a slight anaemia. The haemoglobin was 12.7 g. per 100 ml.; red cells, 3,500,000 per c.mm.; and white cells 3,000 (1,700 polymorphs, 1,000 lymphocytes, 250 monocytes, and 50 eosinophils). Some myeloid arrest was seen on sternal marrow examination, and there was a histamine-fast achlorhydria. Plasma proteins were 8.15 g. per 100 ml., with albumin 3 g. and globulin 5.15 g. (of which 1.9 g. was gamma-globulin) by Cohn's technique. The blood sugar, urea, potassium, sodium, chloride, calcium, and cholesterol were normal, as was the urine examination and the urinary diastase index. A sialogram was suggestive of chronic parotitis, but there was no sialectasis, and *x*-ray films of the chest, skull, and oesophagus were normal.

In October she began treatment with A.C.T.H. in doses of 100 mg. by intramuscular injection. The parotid swellings started to get smaller within a few days, and had disappeared after 10 days' treatment. Parotid secretion analysis showed an increase in amylase content to 38 units per ml., but there was no convincing improvement in the dryness of the mouth or eyes. The gamma-globulin fell to 0.5 g. per 100 ml., and the liver function flocculation tests were improved to ++. Myeloid arrest was no longer seen on repeat marrow films, and the leucopenia disappeared, but all other investigations previously carried out remained unchanged.

When the daily dosage of A.C.T.H. was reduced by stages to 20 mg., the parotid swellings slowly returned, and were again quite pronounced when the A.C.T.H. was stopped after 2,255 mg. had been given over 39 days. Because of this she was given 75 mg. of cortisone daily by mouth in the form of a syrup, and the glands once again regressed. After 750 mg. of oral cortisone had been given in 10 days, the drug was stopped and the patient was discharged.

She was re-examined six weeks later, in January, 1952. The parotid swellings had returned, though not to their original size, and she felt much improved in herself. The eye and mouth symptoms were unchanged, but parotid massage produced a larger amount of clear mucoid secretion with an amylase content of 43 units per ml. A stained smear of the secretion showed some mononuclear and epithelial cells, and a few polymorphonuclear leucocytes. The liver flocculation tests were again ++++, and the leucopenia had returned (polymorphs 2,250 per c.mm.), but there was no other change in the investigations, and the plasma proteins were not altered.

Discussion

The effects of Sjögren's syndrome may be widespread, but in most cases it is the parotid and lacrimal glands which are principally involved. The earliest change in the parotid gland is a disintegration of the glandular parenchyma (Sjögren, 1948). Later there may be atrophy, round-cell infiltration, connective-tissue proliferation, and fibrosis—all manifestations of a chronic inflammatory process of unknown aetiology (Ellman *et al.*, 1951).

In assessing treatment we must remember that the size of the parotid glands may vary spontaneously (Henderson, 1950). This may be due to intermittent blocking of the gland ducts, and at these times the glands may be tender and there may be a slight fever and malaise. However, neither of our cases had shown any marked spontaneous change in size before treatment began.

The disappearance of the parotid enlargements was very striking, though in both cases the swelling started to return when the A.C.T.H. dosage was reduced. In Case 1 small doses of A.C.T.H. over a long period controlled the swellings, while in Case 2 oral cortisone diminished the size of the glands while it was being given. Both patients felt better in themselves, but both said that their eye and mouth symptoms had not been improved. It was of interest that the size of the liver and spleen decreased in Case 1, and that the amylase content of the parotid secretion increased in Case 2.

There have been a few previous reports of similar treatment. Two cases receiving parenteral A.C.T.H. had at least a temporary increase in secretion and diminution in size of the parotid glands (Stephens, 1950; Frenkel *et al.*, 1951). Two other cases similarly treated failed to improve (Offret and Forest, 1950; Fitzgerald *et al.*, 1951). Cortisone used subconjunctivally gave no improvement in Duke-Elder's case (1951).

A temporary beneficial effect on the parotid enlargements has also been reported with deep *x*-ray therapy (Heaton and Shannon, 1948; Ellman and Weber, 1949). The response of the parotid enlargements to both A.C.T.H. and deep *x*-ray therapy is consistent with the presence of a chronic inflammatory lesion. However, this does not help us to identify the cause of the syndrome or to distinguish it from Mikulicz's syndrome, with which it is often confused, since this would probably respond similarly (Heaton and Shannon, 1948).

Summary

Two cases of Sjögren's syndrome are described, one of which had hepato-splenomegaly.

Treatment with A.C.T.H. reduced the parotid swellings to normal size, and the improvement was maintained as long as the drug was given.

There was no improvement in the eye and mouth symptoms.

We wish to thank Professor Sir Henry Cohen and Dr. E. T. Baker-Bates for permission to publish these cases.

REFERENCES

Duke-Elder, Sir Stewart (1951). *Brit. J. Ophthal.*, **35**, 637.
Ellman, P., and Weber, F. Parkes (1949). *British Medical Journal*, **1**, 304.
—— —— and Goodier, T. E. W. (1951). *Quart. J. Med.*, **20**, 33.
Fitzgerald, J. R., Bellows, J. G., Donegan, J. M., Gamble, R. C., Krause, A. C., Mann, W. A., Pearlman, M. D., and Zekman, T. N. (1951). *Arch. Ophthal., Chicago*, **45**, 320.
Frenkel, M., Hellinga, G., and Groen, J. (1951). *Acta endocr., Kbh.*, **6**, 161.
Heaton, T. G., and Shannon, E. H. (1948). *Canad. med. Ass. J.*, **58**, 368.
Henderson, J. W. (1950). *Amer. J. Ophthal.*, **33**, 197.
Offret, G., and Forest (1950). *Bull. Soc. Ophtal. Fr.*, No. 9, 759. Quoted by Duke-Elder (1951).
Sjögren, H. (1948). *Acta med. scand.*, **130**, 484.
Stephens, C. A. L. (1950). *Proceedings of the First Clinical A.C.T.H. Conference*, ed. by J. R. Mote, p. 358. Churchill, London.
Weber, F. Parkes (1945). *Brit. J. Ophthal.*, **29**, 299.

SUDDEN DEATH FOLLOWING AN INJECTION OF PENICILLIN

BY

W. O. THOMSON, M.B., Ch.B., D.P.H.

Late Resident Medical Officer, Belvidere Infectious Diseases Hospital, Glasgow

Allergic reactions to penicillin are not uncommon—Keefer and Anderson (1950) placing them at 1.5–5% of patients treated—and are within the experience of most practitioners. Death due to penicillin therapy, however, is unusual and few cases have been reported.

When a fatal reaction does occur it seems to be due to (*a*) a Jarisch–Herxheimer reaction in known or unsuspected syphilitics; (*b*) severe allergic manifestations, usually occurring after a latent period and slowly progressing to death; or (*c*) anaphylactic shock producing death in a matter of minutes.

Of the few reported deaths attributed to penicillin, only one has been considered anaphylactic. Waldbott (1949) described a patient who, after receiving 50,000 units of penicillin intramuscularly during an acute attack of asthma, reacted immediately with swelling of the mouth, generalized itching, and collapse, with extreme cyanosis and death. She had had penicillin without ill effect several times before, but during the previous month had complained of urticaria and joint pains one week after penicillin therapy. Waldbott thought that the injection must have been intravenous.

O'Donovan and Klorfajn (1946), with an intramuscular injection of 15,000 units of sodium penicillin, produced an anaphylactic-like reaction in a patient known to be penicillin-sensitive. There was a slow recovery over the next two days. Non-fatal anaphylaxis was also reported by Burleson (1950) after the intramuscular injection of 200,000 units of penicillin with procaine.

Other fatal reactions attributed to penicillin sensitivity have been of a more prolonged duration, have frequently involved the skin, and have often occurred after a latent period, during which no signs or symptoms were noted. Thus a case described by Rabinovitch and Snitkoff (1948) developed a maculo-papular rash which progressed to exfoliative dermatitis and death seven days after the last injection of an eleven-day course of intramuscular penicillin. There was a family history of penicillin sensitivity.

Panja and Banerjee (1951) reported a case of an Indian woman who developed blisters of the lip and perineum after penicillin therapy, and who, four months later, had extensive bullae with exfoliation after streptomycin. The condition became very much worse and the patient died when the streptomycin was replaced by penicillin.

Barksdale (1946) reported a case of a sailor known to be sensitive to penicillin who, after his seventh desensitizing dose of 100 units of penicillin, developed a severe cutaneous eruption which progressed to a generalized exfoliative dermatitis, streptococcal septicaemia, and death. A case of Wilensky's (1946) received 30,000 units of penicillin four-hourly in the post-operative treatment of a subtotal gastrectomy. On the fifth day of convalescence the patient had a scarlatiniform rash which later became urticarial. There was a slow deterioration over the next few days, and death ensued.

Berne (1950) described a case in which there was an erythematous rash twenty-four hours after administration of sulphonamides and 30,000 units of penicillin in oil and wax. The condition progressed to an exfoliative dermatitis when the penicillin was repeated, in spite of the fact that the sulphonamides had been stopped. A repetition of the penicillin nine days later, when the skin condition had almost resolved, produced an acute flare-up, leading to generalized exfoliation, purpura, rapid deterioration, and death. Berne was able to demonstrate haemorrhagic necrosis of the bowel mucosa, with a primary lesion in the veins. Penicillin had never been given before.

The only case of fatal hypersensitivity to penicillin recorded in Britain occurred in a 14-months-old child who received "penicillin treatment" for a burn and who died five days later of serous exudation into the pleural cavities, pericardium, and peritoneum (*British Medical Journal*, 1951). Prior to death there had been a history of rash, pyrexia, and swelling of the face. It was not stated whether penicillin had been given before.

Chou and Welply (1949) reported a case in which death occurred two hours after the injection of 40,000 units of penicillin intrathecally as a prophylactic measure.