ACTH IN THE TREATMENT OF RHEUMATIC FEVER

BY

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Since Hench, Kendall, Slocumb & Polley (1949) reported the dramatic effect of ACTH and cortisone on rheumatoid arthritis, an extensive literature has accumulated on the therapeutic effect of these substances in this as well as in other diseases.

Brochner-Mortensen et al. (1949) reported the first case of rheumatoid arthritis treated with ACTH in Denmark. A Danish ACTH preparation was used by E. Vermehren & M. Vermehren (1950) in the treatment of two cases of rheumatoid arthritis and by Schwartz & Sonne (1950) in the treatment of 3 cases of lupus erythematosus disseminatus. In addition Videbæk et al. (1950) have reported 3 cases of rheumatic fever treated with ACTH.

According to the preliminary reports, the effect of ACTH in rheumatoid arthritis appears to be only temporary. Brochner-Mortensen et al.'s patient showed distinct improvement during the treatment, but one week after its cessation, the condition had returned to its former level.

Of the two cases of chronic rheumatoid arthritis treated with ACTH by Vermehren & Vermehren, one failed to show
any definite effect on the joints, whilst a marked clinical improvement occurred in the other case. The duration of this improvement is not stated.

Videbæk et al. (1950) found a dramatic clinical effect with ACTH in two cases of acute rheumatic fever accompanied by severe pericarditis, whilst the effect was more doubtful in the third patient who suffered from atypical rheumatic fever and pancarditis.

In lupus erythematosus disseminatus, Schwartz & Sonne (1950) observed an excellent clinical effect in their first case, a more doubtful effect in the second, and a dramatic clinical effect in the third.

According to the results published up til now, both in Denmark and other countries, the beneficial effect of ACTH in chronic rheumatoid arthritis seems to last only as long as the administration is continued and the patients relapse soon after its discontinuation. It would, therefore, seem justifiable to reserve the small amounts of the drug available in Denmark for diseases which are a danger to life, such as e.g. acute rheumatic fever accompanied by pericarditis or lupus erythematosus disseminatus.

**WRITER’S EXPERIENCE**

In our department, two cases of rheumatic fever have been treated with the Danish ACTH preparation*) and a case of lupus erythematosus disseminatus is at present under treatment**

The treatment in the two cases of rheumatic fever is described below.

*Case 1.* Case rec. 1500/50. Mechanic single, aged 25. At the age of 21 he had had migrating arthralgia unaccompanied by fever. The pains subsided spontaneously.

*) Our thanks are due to Drs. Emil and Martin Vermehren for having kindly supplied the ACTH.

**) This case will be published later.
Fig. 1.
Haematologic, metabolic and hormonal changes during the ACTH administration in Case no. 1.
Seven weeks previous to admission, the patient began to have pain, first in the left thigh, but later in the region of the left loin. At the same time he was subfebrile.

A few days before admission the left knee became painful and swollen. A patellar tap was elicited. The skin was neither red nor warm. Range of motion 30° short of full extension, flexion up to 90°. No tenderness on palpation or movement. Apart from a moderate enlargement of the inguinal and axillary lymph glands, the objective examination failed to reveal anything abnormal.

X-ray of the left knee: Nothing abnormal. Hb. 71 per cent, S. R. 188 mm., AST 40, Mantoux III +, streptococcus agglutination negative, gonococcus complement-fixation test and Wassermann reaction negative. ECG: Tachycardia, otherwise nothing abnormal. X-ray of heart on two occasions: Nothing abnormal. ECGs at weekly intervals during the entire stay in hospital failed to show any signs of myocarditis or pericarditis.

Biopsy puncture of the left knee joint yielded a clear, serous fluid showing no growth either in direct smears or on culture.

The patient remained subfebrile, and anaemic, and showed a constantly raised sedimentation rate (118—83 mm.). After one month the AST had increased from 40 to 500 and remained at approximately this level for the subsequent month. The increase in the AST was accompanied by swelling and pain in the right ankle, later involving both wrists. At the same time the swelling in the left knee subsided. Rheumatic fever was diagnosed, and the patient received acetylsalicylic acid, 1 gm. times daily, iron, ascorbic acid, and short wave diathermy. In addition, he was given penicillin, 300,000 units for 10 days.

As the general condition deteriorated and the joint pains became worse it was decided to try ACTH. The patient was told that it was an experiment.

On Aug. 30, 1950 ACTH (batch N. S. 11) was started as
intramuscular injections, of 5 mg. × 4 daily, for a total of 10 days (see Fig. 1).

After 12 hours, the temperature had returned to normal and the patient stated that he had no pain in any joint. During the subsequent days, the swelling subsided and there was a perceptible improvement in the mobility of the joints affected.

When the treatment was discontinued, both knee joints were still swollen and a patellar tap could be elicited; there was no tenderness on palpation and completely unrestricted mobility.

Ankles, wrists, and finger joints were completely normal. Handshake powerful, slight atrophy of the small muscles of the hand.

After ACTH was withdrawn, there was moderate pain in the right knee joint, but this rapidly subsided, and the patient was allowed out of bed. He was able to walk about without support and was discharged in a satisfactory condition 3 weeks after the treatment had ceased.

Follow-up: Three weeks after discharge the patient appeared for a follow-up examination.

There is still slight swelling of both knee joints, and a patellar tap may be elicited. There is no tenderness on palpation or movements and the other joints are normal.

The patient has been in good health since his discharge from hospital and has now started working. Hb. 91 per cent, AST 160, S. R. 53 mm.

Summary of the Case: A male, aged 25, suffering from rheumatic fever with a characteristic migrating arthralgia, was treated with a total of 200 mg. of ACTH for 10 days. The treatment resulted in definite improvement. The patient has been followed up for 6 weeks after discontinuation of ACTH and remains in good health.

Case II: Case rec. 1661/50. Tailor's apprentice, aged 16, with a history of rheumatic fever with pain in the elbow joints, wrists, and ankles at the age of 11. Treated with a salicylate mixture. ECG: Nothing abnormal. S. R. 80 to 38 mm.
At the age of 13 the patient sustained a fracture of the right tibia. During his stay in hospital a marked systolic murmur was heard, the whole precordium rising en masse during systole.

Ever since, the patient had been in good health until 5 days before admission, when he began to have pain in the left ankle, later involving all the large joints and accompanied by headache, fever, and retrosternal pain. Deep respiration increased the pain. At home he had received a total of 25 tablets of sulphathiazole by mouth, without any effect.

Admitted because his physician had heard pericardial friction murmurs.

On admission the patient was debilitated, pale, cyanosed, and in great pain. Pulse rate 100, temperature 39.3° C. Moderate enlargement of the cervical and axillary lymph nodes. Cardiac auscultation: The heart reached to the second rib, on the right 3 fingerbreadths lateral to the right sternal border, dullness as far as the anterior left axillary line. Pericardial friction murmurs all over the precordium. Normal mobility of all joints, no swelling or redness. S. R. 97 mm., AST 320, Hb. 79 per cent, Mantoux III negative. ECG: raised ST₁ and ST₂: Pericarditis. No abnormal constituents in the urine. X-ray of the heart showed pericarditis with effusion. W. B. C. 13,000, differential count normal.

ACTH could not be obtained immediately, and the patient was therefore treated with penicillin, 300,000 units, acetylsalicylic acid, 1 gm. × 6, vitamins and iron.

This treatment was continued over a period of about 3 weeks without any appreciable effect. The general condition remained poor; there was dyspnoea, cyanosis, and precordial pain. The outlines of the heart remained unchanged at the 2nd rib and the right border 2—3 fingerbreadths to the right of the sternum. There were marked pericardial friction murmurs.

On Aug. 19, 1950, ACTH (batch H. M. 10) was started, 5 mg. × 4 daily, for a total of 10 days (see Fig. 2).

A few hours after the first injection the temperature be-
Fig. 2.
Haematologic, metabolic and hormonal changes during the ACTH administration in Case no. 2.

15°
came normal and the S. R. had decreased from 101 to 3 mm. There was a marked improvement in the general condition and the patient became somewhat euphoric.

The friction murmurs disappeared after a few days and X-ray showed a diminishing cardiac shadow. During treatment with salicylic acid the cardiac shadow increased from 14.5 to 17 cm. (transverse diameter of the chest 24 cm.), but during the administration of ACTH it decreased by 1.5 cm. (Fig. 3). The abnormal electrocardiographic changes disappeared, the T waves gradually becoming positive (Fig. 4).

After ACTH was discontinued, the S. R. rose to 54 mm., but became normal in the course of the following 4 weeks.

Seven weeks after the treatment was stopped the patient was discharged in excellent health.

No complications occurred except for a slightly Cushing-like face (a gain in weight of 3.4 kg. in the course of 6 weeks) and very slight hypertrichosis on the legs.

Summary of the Case: A male, aged 16, was hospitalized

![Fig. 3.](image)

Left picture: Large pericardial effusion in case no. 2 prior to treatment with ACTH. Right picture: Four weeks after ACTH treatment.

The cardiac shadow decreased from 17 cm. to 15.5 cm.
Fig. 4.

Electrocardiographic findings in Case no. 2.
A) Before treatment.
B) After two days' treatment with ACTH.
C) After ten days' treatment.
D) Electrocardiographic findings after seven weeks' treatment.
with rheumatic fever, complicated by pericarditis. On admission he was debilitated, cyanosed, and in great pain.

He received salicylic acid and penicillin for about 3 weeks without any appreciable effect. ACTH, 5 mg. × 4, was then administered for 10 days with a dramatic effect. The patient was discharged in excellent health 7 weeks after ACTH was stopped.

DISCUSSION

The effects of ACTH therapy were studied in two cases of rheumatic fever. Unfortunately, ACTH could not be administered immediately in either case, but the therapy instituted before ACTH proved ineffective in both cases.

In both cases the temperature became normal within 12 hours of the first injection of ACTH.

In Case I there was an almost immediate improvement in the joint symptoms. In Case II there was a marked improvement in the general condition; at the same time the patient showed slight euphoria.

The sedimentation rate dropped from 55 to 6 mm. in Case I, and from 101 to 3 mm. in Case II, during the 10 days of treatment. In both instances, however, there was a considerable rise in the sedimentation rate after the treatment was discontinued.

During the administration of ACTH, both patients exhibited increased urinary excretion of 17-ketosteroids and of reducing corticoids. *)

Serum proteins remained practically unchanged in Case II, whilst Case I showed a slight increase in the albumin as well as in the globulin fraction.

In Case I the haemoglobin content increased from 82 to 89 per cent and the R. B. C. from 3.7 to 4.2 millions.

*) We are indebted to Dr. M. Sprechler of the State Serum Institute, Hormone Department, for having undertaken the hormonal tests.
In Case II the haemoglobin content increased from 72 to 77 per cent, whilst the R. B. C. remained unchanged.

Both patients showed a decrease in the circulating eosinophils, whilst the W. B. C. increased in both cases.

The fasting blood sugar increased in both cases, from 98 to 136 mg. per cent and from 96 to 110 mg. per cent respectively.

The serum potassium dropped from 28.2 to 18 mg. per cent in Case I, and from 35.1 to 15.5 mg. per cent in Case II.

The ECG remained normal in Case I, whilst Case II exhibited first isoelectric and later positive T waves. The rise of ST₁ and ST₂ had disappeared before ACTH was started.

During the administration of ACTH Case I showed a decrease of mucopolysaccharides, consisting mainly of hyaluronic acid, from the connective tissue.*) The number of mast cells also decreased. This test was unsatisfactory in Case II.

Case I also showed a marked decrease in the hyaluronidase inhibitor of the serum**) (antagonistic to bovine testes hyaluronidase) from 3.2 units to 1.2 units per ml. of serum.

After the treatment was discontinued, the amount of inhibitor increased up to 10 units. At the same time the S. R. rose.

Due to an oversight, this test was not performed in Case II.

As compared with the dose used by E. Vermehren & M. Vermehren ours was considerably lower, but the effect was satisfactory. Both preparations (N. S. 11 and H. M. 10), however, appear to have been a good deal more active than stated in the first standardization by the manufactures.

Complications: The intramuscular injections did not result in any untoward effects in either case. Case II, however, developed a Cushing-like face and slight hypertrichosis during the treatment.

*) The histological examinations were carried out at the Department of Anatomy, University of Copenhagen, by Dr. G. Asboe-Hansen.

**) The antihyaluronidase examinations were carried out at the State Serum Institute by Dr. V. Faber.

We wish to express our thanks to both Dr. Asboe-Hansen and Dr. Faber.
SUMMARY

ACTH was administered to two patients with rheumatic fever, complicated in one by pericarditis.

In both cases other methods of treatment had proved ineffective before the administration of ACTH.

Both patients received ACTH, 5 mg. × 4, for 10 days with an excellent clinical effect.

Since ACTH is so scarce in Denmark, it seems worth considering whether it ought not to be reserved for diseases which are a danger to life, such as rheumatic fever accompanied by pericarditis and lupus erythematosus disseminatus.

REFERENCES:


