From the Medical Department A and the Department for Physical Medicine, Rigshospitalet, Copenhagen, and the Hormone Department of the State Serum Institute, Copenhagen.

THE EFFECTS OF ADRENOCORTICOTROPHIC HORMONE (ACTH) IN A CASE OF CHRONIC RHEUMATOID ARTHRITIS

BY

K. BRØCHNER-MORTENSEN, JOH. GEORG, CHR. HAMBURGER, E. SNORRASON, M. SPRECHLER, AA. VIDEBJÆK and TORBEN K. WITH

The etiology of chronic rheumatoid arthritis is still obscure. The disease is far more frequent in women than in men; it is found at all ages, but most frequently in the fourth decade. A hereditary disposition is often found in this disease. Many features in the course of rheumatoid arthritis resemble those of chronic infections: the poor condition of the patient, the raised body temperature, the increased sedimentation rate, the anemia and achlorhydria. The pathological processes in the joints have an «infective» character. It is generally assumed that chilly and humid surroundings favour the outbreak of the disease.

The rheumatoid arthritis has a chronic progressive course, though it seems as if it possesses potential reversibility. Several remedies have been found to induce remissions, especially gold salts. This may also happen following febrile reactions to foreign protein. Transient amelioration has been observed during starvation, after surgical operations and, above all, during the course of hepatitis with jaundice and in pregnancy. The remission frequently starts in the 4th to 6th week.
and disappears at about one month after parturition, independently of the duration of lactation. These observations do not fit in with the microbic theory but suggest the existence of some basic biochemical or hormonal disturbances (for further discussion and references, see: Hench, 1949).

For several years Hench and his collaborators have studied the effect of adrenal cortical extracts on the course of rheumatoid arthritis, and quite recently Hench, Kendall, Slocumb & Polly (1949) have published their astonishing results with Kendall's Compound E (= »Cortisone«) in 16 patients suffering from rheumatoid arthritis. Daily injections of 100 mg. Cortisone, or the acetate of this compound, brought about a marked clinical improvement in all the patients: the muscular and articular stiffness diminished, the articular tenderness and pain on motion were ameliorated. The general state improved, the appetite increased, and several patients experienced a marked sense of well-being. As a rule the symptoms began to recur within two to four days after discontinuation of the treatment. Two of the patients with a severe rheumatoid arthritis were further treated with 100 mg. doses of pituitary adrenocorticotrophic hormone (ACTH). The results of this administration were essentially identical with those resulting from the treatment with Compound E.

These remarkable observations were soon confirmed by other investigators (Robinson et al., 1949; Thorn et al., 1949; and Wolfson et al., 1949).

Reports of the results of biochemical and other analyses carried out during treatment of the patients with compound E are rather scanty. The sedimentation rate decreases, the globulin content of the plasma diminishes. The uric acid excretion increases, and there is a fall in the number of circulating eosinophil leucocytes. ACTH sometimes brings about hypertension, glycosuria, and in one patient acne, hirsutism and amenorrhea occurred and the general appearance of the patient was reminiscent of Cushing's syndrome.

The effects of the various adrenal cortical steroids in the normal human organism have not been described to any great
extent. Recently, the metabolic and biochemical changes obtained by ACTH administration to normal subjects have been thoroughly investigated, e. g. by Mason et al. (1948), Forsham et al. (1948), and Sayers et al. (1949). The most important findings described in these publications are discussed below.

OWN INVESTIGATIONS

As soon as the reports of the effects of Kendall’s Compound E and of ACTH in cases of chronic rheumatoid arthritis had reached Denmark, we decided to try the treatment in suitable cases. The aim of the investigations was to examine the clinical effects of these remedies and to perform as many biochemical, hematological and hormonal analyses as possible. It proved to be impossible to obtain the preparations from U. S. A., but through the courtesy of Dr. Frederik Paulsen, Nordiska Organon, Stockholm, we were given an amount of Cortrophin (ACTH), sufficient to carry out the first of the planned experiments.

Material and methods.

The ACTH preparation used was of porcine origin. With the permission of the makers some of their assay results are reported below. The activity of the preparation was determined by Sayer's method (see: Sayers, Sayers & Woodbury, 1949) and gave the results summarized in Table 1.

Table 1.
The potency of the Cortrophin preparation used in the present investigation. By the courtesy of Organon.

| Dose in γ per 100 gm. body weight | Mean ascorbic acid decrease, in γ per 100 mg. adrenal*
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0.33</td>
<td>46</td>
</tr>
<tr>
<td>1.0</td>
<td>76</td>
</tr>
<tr>
<td>3.0</td>
<td>125</td>
</tr>
<tr>
<td>9.0</td>
<td>143</td>
</tr>
</tbody>
</table>

*) The figures in this column represent the average result from 20 hypophysectomized rats.
In human subjects a 50 to 80 per cent decrease in the number of cosinophil leucocytes occurred after a single injection of 25 mg. of the preparation. It possessed a slight pressor activity (0.02—0.04 I. U. per mg.) and a slight oxytocic activity (0.02 I. U. per mg.) Prolactin was not demonstrable.

**Blood sugar** was determined by the method of Hagedorn & Norman Jensen (1923); **total plasma proteins**, by the technique of Henriques & Klausen (1932). The electrophoretic examinations of the plasma proteins were carried out in the State Serum Institute with the Tiselius apparatus by the biochemist Mr. Birch Andersen.

**Uric acid** was determined by the uricase method of Prætorius (1949); **cholesterol in serum** by a modification of Brun's technique (1935). For the determination of **sodium in serum** the method of Birerring & Nielsen (1948) was used; and **plasma bilirubin** according to With (1943).

**Urinary 17-ketosteroids** were assayed by Hamburger's micro-method (Hamburger & Rasch, 1948). The glucocorticoids in the urine were measured by the glycogen deposition test; the procedure of Venning, Kazmin & Bell (1946) was strictly followed. The standard curve given by these investigators was used for the calculation of the »glycogenic units«, as the lack of Kendall's Compound E made it impossible for us to establish our own calibration curve. This procedure seems justifiable, as the values found in our case before and after ACTH administration agree with the normal values of Venning et al. In any case, the relative values for the excretion from day to day must be fairly accurate. The urinary reducing corticoids were measured by the method of Heard & Sobel (1946) and Heard, Sobel & Venning (1946), modified by Sprechler (1949).

**Case record.**

M. L.-R. J. No. 968/49 53 years old married woman. 3 pregnancies, no abortions. 1913 appendectomy. 1921 tonsillitis and otitis media complicated with mastoiditis. 1923 operation for
uterine prolapse. 1924 otitis media. Since 1935 the patient had suffered from a progressive chronic rheumatoid arthritis and was repeatedly admitted to hospitals. She was treated with gold salt four times, last treatment in 1947.

Admitted at Rigshospitalet, Med. Dept. A, on Jan. 31, 1949. The following three months she was treated with physical therapy but with only little success. Before the treatment with ACTH the patient showed a typical rheumatoid arthritis in advanced stage. There were pain, stiffness, and capsular swelling of the following joints: shoulders, elbows, hands, metacarpal, interphalangeal, knees, ankles, and metatarsophalangeal. The right fingertips failed to reach the palm by 1 cm. in maximal flexion and those of the left hand 5 cm. She was unable to move a spoon to her mouth with the right hand, could not brush her hair, and walked with great difficulty. Furthermore there was an infiltration of fibrous tissue as large as the palm in the left trochanteric region; even the most energetic physical treatment had been unable to lessen or remove this.

From June 25th she received daily intramuscular injections of ACTH, the doses being gradually increased from 25 mg. to 100 mg. After two injections of 100 mg. the dose was diminished to 75 mg. which was given for 5 days; she then received 50 mg. daily for 4 days and finally one injection of 25 mg. Altogether she received 950 mg. ACTH in the course of 15 days. The preparation was given as a single injection in the morning, with one exception, the last 100 mg. dose being divided into two. Later on the patient was treated with daily injections (i. m.) of testosterone propionate in oily solution. When not injected with these remedies, the patient received daily placebo injections of saline.

Clinical findings.

As early as one day after the beginning of the treatment a remarkable subjective improvement was noticed. The articular and muscular functions improved, and in the course of the following days the swelling of the joints decreased. Hy-
drops developed in the knees followed by well marked streptococcus localized to the capsule tissue; also the tissue of other joint capsules became smoother and less tender. The circumference of the right ankle-joint was decreased by 2.5 cm., and the strap of her wrist-watch had to be considerably tightened. In the course of a few days she was able to give a firm grasp of the hand and to clench her fist. Shortly afterwards she was able to climb stairs. After the twelfth injection she was able to produce a work performance of 400 kgm./min. for some minutes on bicycle-ergometer. The infiltration of the left thigh disappeared completely, and the 36-year-old appendectomy scar became tender and narrower. Two days after the last injection, the symptoms recurred. The articular pains, tenderness, stiffness and swelling reappeared and in the course of one week the state of the patient was as before the treatment, furthermore the fibrous infiltration gradually returned. Slight feeling of pressure in the chest and hot flushes were the only untoward reactions observed. The blood pressure, pulse rate, body temperature and body weight did not change significantly. The subsequent treatment with testosterone propionate had no effect whatever on her symptoms.

*Laboratory findings* (see Figs. 1 to 3).

The *urinary output* averaged 750 ml./24 hours, with the usual day-to-day variations. The *fasting blood-sugar* was slightly raised from the day after the first injection and remained somewhat unsteady up to one week after the last injection. The maximal fasting value was 158 mg. per cent. *Glycosuria* appeared for some days, the maximal excretion of sugar being 5 gm./24 hours. *Ketonuria* did not occur.

The *total plasma proteins* decreased during the treatment from about 9 to 7 gm. per cent. The albumin fraction was unchanged; the globulin fraction decreased from about 4 to 2.3 gm. per cent. By electrophoretic examinations the decrease was found to be due to a diminution of the \( \gamma \)-globulins. The decrease persisted for some days after discontinuation of the treatment. Testosterone propionate had no effect on the plasma proteins.
Fig. 1.
Hematologic and metabolic changes in the present case.
Fig. 2.

Metabolic changes in the present case.
Nitrogen balance. The patient was put on a constant diet, the protein content of which was determined. The excretion of nitrogen in the urine and stools was measured. During treatment there was a negative nitrogen balance, followed by a post-treatment period of positive balance.

Uric acid in serum increased from about 1.5 to 3.8 mg per cent during the ACTH administration and for a few days afterwards; it then gradually decreased. During and after the treatment with testosterone propionate the values were slightly increased. The uric acid excretion was somewhat difficult to evaluate, as the pre-treatment observation period was rather short; a moderate increased excretion occurred during the treatment. The patient was not put on a purine-free diet.

The content of cholesterol in serum showed an initial increase, followed by a decrease to normal values. A gradual increase subsequently occurred, beginning during the last days of the injection period and reaching a plateau about two weeks after the last injection.

The basal metabolic rate was rather constant at 90 per cent, probably exhibiting a slightly falling tendency during and shortly after the treatment.

Potassium, sodium, and chloride. A marked fall in the potassium content of the serum occurred during the treatment with ACTH from 17.3 to 10.9 mg per cent. The sodium content likewise decreased, whereas the decrease in chloride was insignificant. No changes in the electrolytes were observed during the testosterone propionate treatment.

Hematologic examinations. The blood sedimentation rate decreased from 28 to 7 mm. during the administration of ACTH, but afterwards rose to 60 mm. There were no significant changes in the hemoglobin content or in the erythrocyte content. The hgb. was about 80 per cent but when the patient got worse after discontinuation of the treatment, the hemoglobin gradually fell to 50 per cent and then slowly increased. The blood platelet count was constant. The number of circulating polynuclear leucocytes varied apparently independently of the injection period; the eosinophil leucocytes decreased a
little, but no significant changes in the number of the lymphocytes were noticed.

The bilirubin content of plasma was rather constant (0.20 to 0.30 mg. per cent). A transient increase (up to 0.58 mg. per cent) occurred following treatment.

Sero logic examinations. The anti-streptolysin titer remained low during the whole observation period. The streptococcal agglutination titer decreased from 1:640 to 1:160 during the ACTH administration, but marked variations had occurred during the preceding months.

The electrocardiogram. Slight changes were seen in the terminal complexes. The duration of systole was prolonged a little, but not to a pathological degree.

The 17-ketosteroid excretion was low in the periods when no injections were being given. The average value (2.7 mg./24 hours) was half the normal average for a woman of her age and at the lower limit of the normal range (Hamburger, 1948). Immediately after the beginning of the injections the excretion increased simultaneously with the increasing doses of ACTH. The increase continued for a couple of days after a diminution of the daily dose to 75 mg.; a first maximum (16.5 mg.) occurred on the 8th day of the treatment, but then the excretion decreased to 9.1 mg. The treatment was continued with smaller doses (50 and 25 mg. per day) and another steep rise occurred, the highest value (17.9 mg./hours) being observed on the first day after the last injection. In the course of the next 24 hours the 17-ketosteroid excretion had fallen to almost pre-treatment level. During the treatment with testosterone propionate (25 mg. daily for 14 days) the excretion increased and reached a maximum (9.2 mg.) on the 7th day, then gradually declined.

Separation of α- and β-17-ketosteroids by the digitonin precipitation method of Frame (1944) was performed on several of the urines. The average percentage of β-fractions was 4.4 during ACTH administration; in the period without any treatment the figure was 1.7; during the testosterone propionate administration the β-fractions averaged 1.2 per cent.
Mason et al. (1948) found no digitonin precipitable fraction in their extracts.

The urinary excretion of reducing corticoids was examined from the third day of the treatment period. The excretion curve showed a remarkable resemblance to that of the 17-ketosteroids, i.e. two peaks (at 3.76 and 4.25 mg./24 hours, respectively) and a period of low excretion between them. The second maximum occurred on the first day after discontinua-
tion of the ACTH administration but the next 24-hour urine contained only 0.44 mg./24 hours. The excretion was somewhat irregular during the next two weeks. Treatment with testosterone propionate was not accompanied by any increase in the content of reducing corticoids.

The glucocorticoid excretion agreed so closely with the values obtained chemically that a description of the excretion curve would be a mere repetition. In the course of 24 hours the excretion fell from the second maximum (375 glyc. units) to above one tenth of this value. The daily variations in the post-treatment excretion were less marked than those observed with the chemical method.

DISCUSSION

The clinical improvement of the patient during the administration of ACTH was very remarkable. In no respect did it differ from the results reported by Hench et al. (1949), the symptoms promptly recurring when the treatment was discontinued.

The changes observed in the composition of the blood and urine during the ACTH administration were, in most instances, of the same nature as those reported by Mason et al. (1948), Forsham et al. (1948) and Sayers et al. (1949) viz., a decrease in the sedimentation rate and in the number of eosinophil leucocytes, negative nitrogen balance, hyperglycemia, glycosuria, a decrease in the amount of potassium in the serum, and an increase in the uric acid concentration. Further comparative data are given in Table 2. The excretion of 17-ketosteroids, reducing corticoids and glucocorticoids increased considerably, the maximal values being 6—7 times the average control value for the 17-ketosteroids and the reducing corticoids, while the maximal excretion of the glucocorticoids exceeded the average control value by 15 times.

These observations seem to indicate that a stimulation of all the multiple functions of the adrenal cortex had taken place. The effects of the ACTH treatment were confined to
the period of treatment and to the first two days after discontinuation of the injections. In this respect no difference seems to exist between the "stimulation therapy" with the hypophyseal "trophic" hormone and the "substitution ther-

Table 2.

Biochemical and hematologic effects in man during administration of adrenocorticotrophin. Comparison of data from the literature with those of the present investigation.

<table>
<thead>
<tr>
<th>Laboratory examination</th>
<th>Mason et al. (1948)</th>
<th>Forsham et al. (1948)</th>
<th>Sayers et al. (1949)</th>
<th>Present case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary 17-ks.</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urinary glucocorticoids</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Total urinary nitrogen</td>
<td>(+)</td>
<td>(—)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urine acid in urine</td>
<td>+</td>
<td>+</td>
<td>+ (?),</td>
<td>+</td>
</tr>
<tr>
<td>Uric acid in serum</td>
<td>0</td>
<td>(—)</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Blood sugar</td>
<td>+</td>
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<td></td>
<td></td>
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<tr>
<td>Glucose in urine</td>
<td>0</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Plasma cholesterol</td>
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<td>—</td>
<td>—</td>
<td>+</td>
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<tr>
<td>γ-globulins</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>CO2 in plasma</td>
<td>+</td>
<td>(+)</td>
<td>0</td>
<td></td>
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<tr>
<td>Potassium in plasma</td>
<td>0</td>
<td></td>
<td>—</td>
<td></td>
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<tr>
<td>Potassium in urine</td>
<td>0</td>
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<td>+</td>
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<tr>
<td>Sodium in plasma</td>
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<tr>
<td>Sodium in urine</td>
<td>0</td>
<td>(—)</td>
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<tr>
<td>Chloride in plasma</td>
<td>0</td>
<td></td>
<td>0</td>
<td>(—)</td>
</tr>
<tr>
<td>Chloride in urine</td>
<td>0</td>
<td>(—)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>—</td>
<td>—</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Eosinophil leucocytes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

1) Normal young woman, daily i. m. injections of 25—100 mg. ACTH.
2) Normal and pathol. cases. Single and repeated i. m. injections of ACTH.
3) Two normal men. Single intravenous infusion of 50 and 100 mg. ACTH.
4) 53 years old woman with rheumatoid arthritis. Repeated i. m. injections.

0 = no change; + = increase; — = decrease
(+ ) = slight increase; (— ) = slight decrease.
rapy» with the cortical hormone, a fact which emphasizes the special nature of the hypophyseal-adrenal relationship.

The well marked two-peak excretion curves for 17-ketosteroids and corticoids raises certain questions. The remarkable agreement of the three curves (see Fig. 3) rules out the possibility that the cause might be sought in technical variations involved in the analytical procedures. They must undoubtedly reflect important changes in the production and secretion of steroids by the adrenal cortex. A study of the mechanism of the hypophyseal-adrenal relationship, recently summarized by Sayers & Sayers (1948), seems to offer a reasonable explanation of the phenomenon.

ACTH acts as a catalyst in the series of reactions involved in the transformation of cholesterol to cortical hormones. A depletion of sudanophil substance, cholesterol and ascorbic acid from the cortex takes place (Long, 1947, and Ducommun & Mach, 1949). In the present case the first seven injections (25, 50, 75, 100, 100, 75 and 75 mg., resp.) accelerated the production of the cortical hormones at a rate far exceeding the restoration of precursors of the hormones. The secretory capacity of the cortex is consequently exhausted, and the production, release and excretion of the hormones decrease in spite of continued ACTH administration. It is not unlikely that a continuation of the high doses might have resulted in a complete and fatal break-down of the cortical functions. Before the excretion had reached the minimum, the daily dose of ACTH was, however, decreased to 50 mg. per day for 4 days and then to 25 mg. (the last injection). At this dose level the rate of new formation of cholesterol ester exceeds that of the production and release of cortical hormones, allowing the cortex to recover. It is reasonable to assume that the ACTH injections have produced a hypertrophy of the cortex, and that the hypertrophied cortex was able to respond to the ACTH stimulation; the second maximum in the steroid excretion thus reflects the increased production and secretion of cortical hormones.

During the treatment with testosterone propionate the uri-
nary 17-ketosteroid excretion increased. An additional excretion of about 70 mg. took place, and it could be calculated (according to Hamburger & Kaae, 1949) that about 24 per cent of the testosterone propionate injected had been excreted as 17-ketosteroids. The additional excretion of 17-ketosteroids during the ACTH administration amounted to about 118 mg. From these figures it can be calculated that the ACTH treatment has had the same effect upon the 17-ketosteroid excretion as the injection of the total dose of about 600 mg. of testosterone propionate.

During the administration of testosterone propionate the only significant effect observed was the increased 17-ketosteroid excretion. As all the other changes brought about by the ACTH administration were absent or insignificant, it may be concluded that the hematological and metabolic changes cannot be due to the 17-ketosteroids or their precursors, but must be produced by an increased elaboration of other adrenal cortical steroids.

SUMMARY

A 53 years old woman suffering from severe chronic rheumatoid arthritis of 14 years' duration was treated with adrenocorticotropic hormone (ACTH) for a period of 15 days. The total dose was 950 mg., the daily dose varying between 25 and 100 mg.

The clinical effects closely resembled those reported by other investigators. The articular swellings, pain and tenderness on motion rapidly diminished. The articular and muscular functions were remarkably improved. During the treatment she could get out of bed, walk without pain, and climb stairs unaided. Her appetite improved, and she experienced a feeling of well-being. A remarkable effect on the fibrous tissue was observed. The blood sedimentation rate decreased, the total plasma protein decreased, due to a diminution of the \( \gamma \)-globulins. There was a negative nitrogen balance and an increase in the uric acid concentration in the serum. Hyper-
glycemia and glycosuria occurred. The serum potassium and sodium decreased. The number of circulating eosinophil leukocytes decreased.

The urinary excretion of 17-ketosteroids, reducing corticoids and glucocorticoids increased 6 to 15 times. The excretion curves for these substances were remarkably alike and exhibited two maxima and an intervening depression. This peculiar excretion pattern was thought to be due to a temporary exhaustion of the cortical functions, caused by an over-stimulation by the 100 mg. doses of ACTH.

A few days after discontinuation of the treatment the symptoms of the disease reappeared and the laboratory findings returned to pre-treatment conditions. The only effect of a subsequent treatment with 350 mg. testosterone propionate for 14 days was an increased output of 17-ketosteroids.

REFERENCES

Frame, E. G.: Endocrinology 34, 175, 1944.


