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ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE: THEIR EFFECT ON INTRADERMAL REACTIONS

By

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INTRODUCTION

In 1949 Eriksson-Lihr *et al.* published their results on the significance of the suprarenal gland cortex on allergic diseases. They discovered that 17-ketosteroids in the urine of 24 allergic patients gave abnormally low values.

The experiments of Forsham and Hill on the effect of ACTH and cortisone on circulating eosinophils in the blood lead them to undertake a series of experiments to see the value of these drugs in heating allergic complaints.

Bordley *et al.* were the first to publish results on the treatment of five patients suffering from bronchial asthma with ACTH. Daily intramuscular injections of from 30-300 mg ACTH were given for a period of 11-21 days. The entire dosage totaled 360 to 775 mg. All symptoms disappeared within a short time.

A few months later Rose *et al.* submitted their results of treatment with ACTH of six patients with bronchial asthma. The patients were carefully selected, all of them being severe cases and all having been under observation and treatment for a period of three years prior to these experiments. They were given dosis varying from 150 to 75 mg. ACTH per day. Within 48 hours all symptoms disappeared from four pat-

ients, while in the case of the last two, the symptoms did not entirely disappear. Observations made two weeks later revealed pronounced new symptoms in all the patients. It appeared, furthermore, that the eosinophils in the blood were in 24 hours reduced to about zero, and that histamine disappeared from the urine during the treatment.

Randolph *et al.* measured the results of ACTH treatment by its effect on respiratory capacity. After one days treatment the capacity showed an increase.

Carey *et al.* treated 19 patients suffering from severe bronchial asthma with ACTH; 15 of them showed complete subjective and objective recovery, while the remaining 4 showed over 50 % improvement. The treatment lasted from 4 to 21 days. A total quantity of ACTH from 190 to 1928 mg was given. Five patients with bronchial asthma were treated intramuscularly with cortisone. However, the symptoms disappeared completely from one patient only. Four patients were given 200 mg, on the first day, thereafter 100 mg per day, while the fifth patient, from whom the symptoms disappeared, was given 300 mg on the first day and thereafter 200 mg. per day. From these experiments it appears that ACTH has a better effect than cortisone on the treatment of asthma. Simultaneously, Carey *et al.* examined the immediate cutaneous reactions (dust and pollen) and found that they were in most cases partially or completely reduced during the ACTH treatment. In five patients showing typical immediate reactions to dust and pollen, four demonstrated a clear reduction of these reactions while treated with ACTH. In the case of the fifth patient no changes could be observed. In four patients treated with cortisone a reduction of the cutaneous reactions was found, though not as pronounced as in the case of ACTH treatment. Thereafter, they were also given ACTH, and skin reactions were further reduced.

From the Allergic Clinic of the "Sahlgrenska Sjukhus" Gothenburg, Arnoldsson and Pipkorn reported on the treatment with ACTH of four bronchial asthma patients. Also in

these cases a pronounced improvement of all asthma symptoms was found after 24 hours, and complete disappearance of all subjective and objective symptoms after 48 hours. In the case of three of these patients, recovery lasted more than 2 months, while the fourth showed no symptoms for a little more than one week only.

Zeller *et al.* examined the effects of ACTH on skin reactions of allergic patients. Contrary to Carey *et al.* they found no change in skin reactions with ACTH treatment. Cutaneous injections with a mixture of 2/3 ACTH and 1/3 pollen gave the same reactions in spite of the addition of ACTH.

E. Schwartz was the first to publish in January 1951 the possibility of orally treating bronchial asthma with cortisone acetate. He treated three patients with severe bronchial asthma, giving them from 100 to 200 mg per 24 hours. One hour after the second oral cortisone acetate dose the patients were relieved of asthma symptoms. With three patients no secondary effects or toxical symptoms were observed. At the finish of the oral cortisone acetate treatment symptoms were inclined to return earlier than after intramuscular treatment.

Soon after this article followed the report of Salén from Stockholm on treatment of bronchial asthma with ACTH combined with orally administered cortisone acetate. The latter was used as a maintenance dose after final ACTH treatment. He reports on one case of bronchial asthma, which was first treated with comparatively small doses of ACTH: 10 mg $\times$ 4 during six days, thereafter 5 mg $\times$ 4 during 10 days, then 5 mg $\times$ 2 during two days, then 5 mg $\times$ 1 during 5 days, afterwards he gave cortisone orally 25 mg $\times$ 2 during 2 days, then 25 mg $\times$ 1 during 4 days, and finally 25 mg every two days. The patient was free from symptoms after 3 days of ACTH treatment, however, the patient had to take diminishing doses of adrenaline until the 14th day after the beginning of the treatment. During this treatment no secondary effects, signs of retention of

water, nor changes in carbohydrate metabolism were registered. Blood pressure remained unchanged. Salén believes this makes feasible the treatment of severe cases of chronic bronchial asthma, which were previously untreatable. He also reports a case of severe asthma, which after treatment with ACTH showed no symptoms for 18 months.

Leith *et al.* gave ten hay fever patients 20 mg of ACTH intramuscularly every 6 hours for 8 doses. ACTH in the dosage and time interval outlined did not significantly alter the positive scratch or passive transfer skin tests.

Feinberg *et al.* reported on 15 bronchial asthma patients treated with ACTH and cortisone acetate, and four patients with hay fever, treated with ACTH. They examined the immediate reactions with dust and pollen and discovered, as did Zeller *et al.* and Leith *et al.* and contrary to Carey *et al.*, no changes in the intradermal reactions during ACTH and cortisone treatment. They also investigated whether the sensitivity towards intradermal histamine changed during treatment with ACTH and cortisone and found that it did not.

The above reports demonstrate indisputably that ACTH and cortisone, the latter both as injection and as oral treatment, have a pronounced effect on allergic diseases particularly on bronchial asthma. Therefore, an investigation has been planned, in the hope of attaining a deeper understanding of allergic problems by examining the effects of ACTH and cortisone on allergic persons.

This article is a preliminary report. Besides the above mentioned review, interest has particularly been concentrated on the intradermal reactions during treatment with ACTH and cortisone, because, as mentioned, contradictory viewpoints have been set forth, Carey *et al.* finding a reduction in the immediate skin reactions, and Zeller *et al.*, Feinberg *et al.* and Leith *et al.* finding unchanged reactions during cortisone and ACTH treatment.

CLINICAL FINDINGS

As this article concentrates on the allergic intradermal reactions, patients with particularly pronounced reactions were selected. The treatment comprised outpatients contrary to the cases mentioned above, all of whom were in-patients. The first task was to examine whether the skin reactions diminish simultaneously with the fall of the eosinophils in the blood.

A dose of 50 mg ACTH was given to a patient with bronchial asthma (dust allergy) with positive intradermal reaction to acetone-precipitated house dust.

In the Allergy Consultation the diameter of the weals and extent of redness of intradermal reactions we measured in millimetres and pseudopodia are indicated by a plus or minus sign.

Before the patient was submitted to treatment with

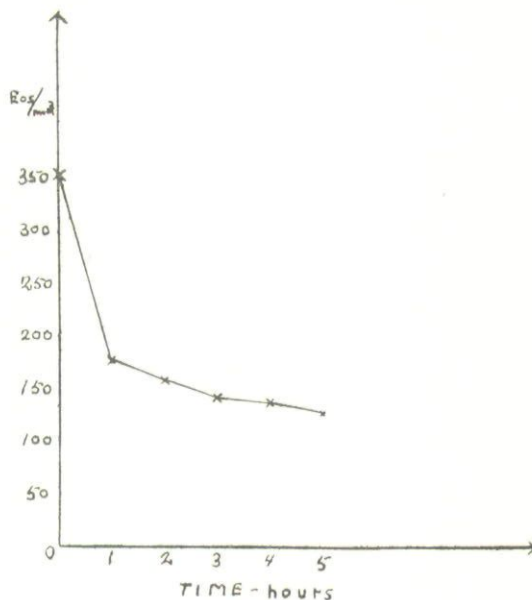


Diagram 1

Eosinophils in the blood after one injection of 50 mg ACTH.

TABLE I

Intradermal reactions to house dust extract before and after treatment with ACTH 50 mg

Concentration	Before given ACTH	1 hour later	2 hours later	3 hours later	4 hours later	5 hours later
	wheel in mm	Eryth- ma in podia mm				
1/10000000	—	20	—	20	—	—
1/1000000	5×5	20	5×5	30	5×5	30
1/100000	6×6	30	6×6	30	6×6	30
1/10000	9×10	30	10×10	30	10×11	30
1/1000	11×10	30	10×10	30	9×12	30
1/100	15×13	30	11×15	30	12×13	30

TABLE II

Intradermal reactions to histamin before and after treatment with ACTH 50 mg

Concentration	Before given ACTH	1 hour later	2 hours later	3 hours later	4 hours later	5 hours later
	wheel in mm	Eryth- ma in podia mm				
1/10000000	5×5	30	5×5	30	5×5	30
1/1000000	6×6	30	5×7	30	6×6	30
1/100000	8×7	30	8×8	30	7×8	30
1/10000	10×5	30	10×8	30	10×10	30
1/1000	11×10	30	10×12	30	12×14	30
1/200						
1/100						

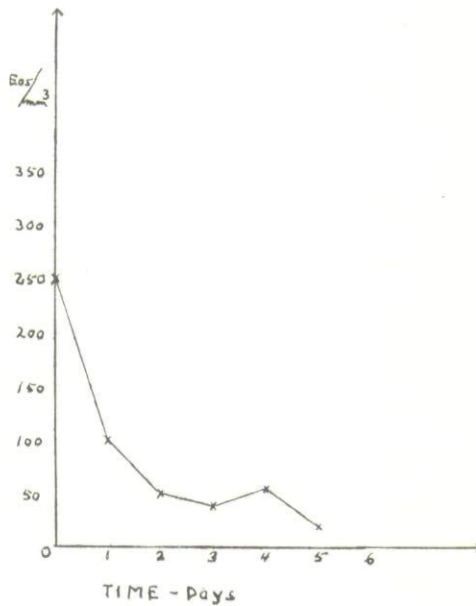


Diagram II

Eosinophils in the blood during treatment with ACTH 50 mg daily
(dust patient).

ACTH, intradermal reactions were made in the previously described way with purified dust and with histamine in the concentration of 1:10000000 to 1:100. Also the eosinophils in the blood were counted according to R. Dunger's method (H. A. Andersen's modification).

After treatment hourly skin tests with house dust and histamine were made, the eosinophils cells in the blood being counted simultaneously. The results recorded in table 1 and 2, show that the skin reactions to histamine and house dust five hours after were completely unchanged. As shown on diagram I, the eosinophils cells dropped to 50 % of the original value during the first hour of the treatment.

It was decided to determine whether a continuous dosage for a longer period, such as for five days, would change the skin reactions.

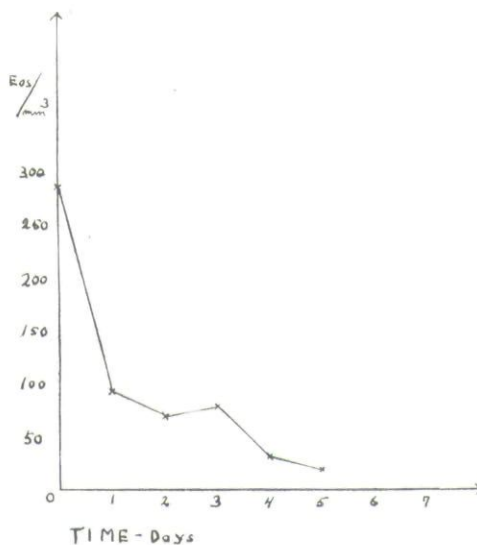


Diagram III

Eosinophils in the blood during treatment with ACTH 50 mg daily.

Two patients suffering from bronchial asthma were selected, one of them sensitive to dust, and the other to dust and pollen. For five days doses of 50 mg ACTH were given in one injection daily to each patient.

Before the first injection skin tests were made on the first patient with dust and histamine, and on the other patient with pollen and histamine in concentrations of 1:10000000 to 1:100 in the manner indicated above. Simultaneously the eosinophils in the blood were counted.

Daily thereafter at the same hour and immediately preceding the new ACTH injection the skin tests were made and the eosinophils were counted.

Both patients after the first 24 hours treatment, exhibited a pronounced improvement in their symptoms. One of the patients, living on 4th floor, stated that, for the first time in many years, she was able to walk up the stairs without becoming short of breath. No secondary effects were ob-

served, apart from a slight retention of water. The blood pressure, which was measured daily remained unchanged. As indicated in table 3 and 4 no ascertainable changes in the intradermal reactions to dust and histamine could be traced. The eosinophils cells fell as indicated in diagrams II and III.

Next two patients suffering from bronchial asthma with positive house dust reactions were treated with cortisone in order to investigate whether this substance would influence the cutaneous reactions.

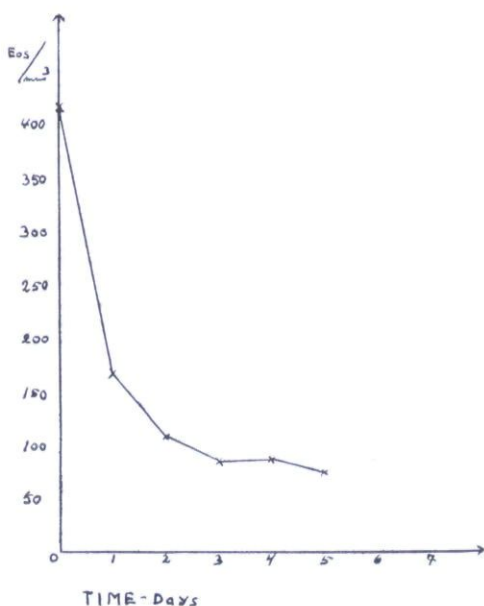


Diagram IV

Eosinophils in the blood during treatment with cortisone 100 mg daily (Patient I).

Each patient was given 200 mg cortisone orally during five days. Skin tests with house dust and histamine were made daily, and eosinophile cells were counted daily. No changes were traced in the intradermal reactions during the

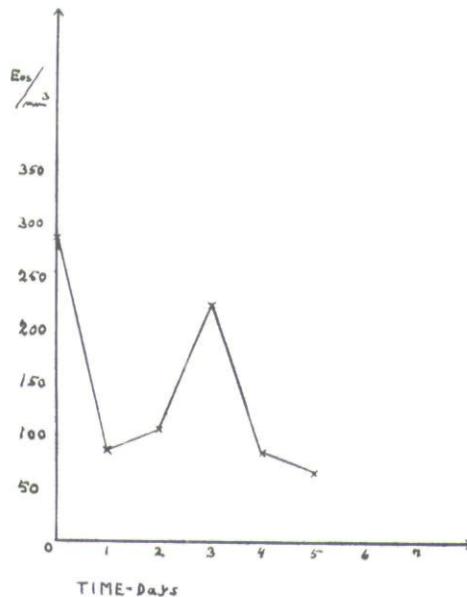


Diagram V

Eosinophils in the blood during treatment with cortisone 100 mg daily (Patient II).

five days of treatment. Clinically, the patients in these cases showed improvement in 24 hours. However, on the third day of treatment one of the patients had respiratory difficulties and some cough. As indicated in diagram V higher number of eosinophils in the blood was found on that day, which indicates a correlation between clinical improvement and decline of the number of eosinophils in the blood. No secondary effects of any kind were observed in any of the patients.

Zeller *et al.* examined the content of eosinophils in the skin before and after injection of ephedrine, and found that the number of eosinophils declined considerably 15 minutes after the injection. As it might be supposed that the number of eosinophils contained in the skin may influence the extent of intradermal reactions, the two cortisone treated patients

TABLE V
*Intradermal reactions with house dust extract on the two cortisol treated patients
 before and after adrenaline 0.5 ml subcutaneously*

Concentration	Patient I			Patient II		
	Before given adrenaline	Erythema in mm	pseudopodia	After given adrenaline	Before given adrenaline	After given adrenaline
1/10000000						
1/1000000	5 × 5	20	—	—	5 × 5	—
1/100000	5 × 5	30	—	—	5 × 5	—
1/10000	8 × 8	30	—	5 × 5	8 × 8	—
1/1000	10 × 8	30	—	6 × 6	10 × 11	6 × 6
1/100	10 × 10	30	+	7 × 7	10 × 11	5 × 5
					11 × 12	8 × 8
						only faint redness

were given 0.5 ml adrenaline subcutaneously. Skin tests with house dust were done before and 30 minutes after giving adrenaline. The results are given in table 5 and they show a clear reduction of intradermal reactions after adrenaline.

DISCUSSION

Even if the material presented is small it is evident that ACTH and cortisone alone will not produce any change in the intradermal reactions of allergic patients or any change in the sensitivity towards histamine.

The reduction of the cutaneous reactions after injection of adrenaline may be traced to the fall in eosinophils in the skin. This is based on the theory that antigen-antibody reaction destroys eosinophils cells and releases their histamine which produces the allergic reactions.

A further discussion and examination of this problem will appear later.

SUMMARY

- 1) A review is given of the literature on ACTH and cortisone employed in the treatment of bronchial asthma.
- 2) It is found that ACTH and cortisone will not change the urticarial cutaneous reactions or the sensitiveness to histamine.
- 3) It is found that a reduction of the cutaneous reactions takes place in cortisone treated patients after subcutaneous adrenaline injection.

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