Ann. rheum. Dis. (1968), **27**, 7

HYPOTHALAMO-PITUITARY-ADRENAL FUNCTION IN PATIENTS ON LONG-TERM ADRENOCORTICOTROPHIN THERAPY

BY

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Adrenocorticotrophic hormone (ACTH) is of value in the treatment of a number of diseases which respond to corticosteroid therapy, and has been preferred to corticosteroids themselves by several clinicians on the grounds that side-effects are fewer and withdrawal easier (Savage, Copeman, Chapman, Wells, and Treadwell, 1962), that there is a better clinical response in rheumatoid arthritis (West, 1957), and that there is no growth retardation in children (Friedman and Strang, 1966).

The suppressive effect of prolonged corticosteroid therapy on the hypothalamopituitary-adrenal (HPA) axis has been well-documented, and the danger that patients so treated may have an inadequate response to stress is universally recognized. Whether a similar risk of suppression exists after ACTH therapy is less clear. Severe operative shock has been reported (Hayes and Kushlan, 1956) but there are far fewer reports of such shock following ACTH than following corticosteroid therapy. This may be because ACTH is a less common form of treatment or it may indicate that ACTH is inherently less likely to cause suppression.

ACTH is used frequently in this department for the treatment of rheumatoid arthritis with good clinical results (Savage, Davis, Chapman, Wickings, Robertson, and Copeman, 1959). Pituitary-adrenal function in twelve ACTH-treated patients has been assessed by the metyrapone test, with only one abnormal result (Savage and others, 1962). Holub, Wallace, and Jailer (1960) also found a normal response in all of six patients tested but acute suppression of the metyrapone response has been reported in normal subjects given short-term high-dosage ACTH therapy (Solem and Brinck-Johnsen, 1961; Plager and Cushman, 1962).

Several different tests of pituitary-adrenal function have been developed in addition to the metyrapone test, and it is now recognized that no single test can adequately assess the functional integrity of the entire HPA axis. These tests have been used to assess corticosteroid-treated patients and patients on intermittent ACTH therapy (Nelson, Mackay, Sheridan, and Weaver, 1966), but their use has not been reported in patients on long-term daily ACTH therapy. It was therefore decided to investigate a group of such patients using a variety of test procedures in each subject, as it is important to elucidate the effect of long-term ACTH therapy on the HPA axis.

Material and Methods

31 patients with rheumatoid arthritis were investigated, but two of them had only the diurnal variation test. All had been treated with a single daily subcutaneous injection of ACTH (Acthar Gel*) for from 2 weeks to 14 years (Table, overleaf).

Two patients had stopped this form of therapy, for 1 year and 18 months respectively, before testing. The remainder were still receiving ACTH, although some from whom ACTH therapy was being gradually withdrawn were tested while receiving less than their previous therapeutic maintenance dose. The usual maintenance dose was between 20 and 40 units daily. The dose was not changed during the period that the tests were performed. None of the patients had at any time received oral corticosteroids.

The following investigations were carried out:

Synacthen Test

The adrenal response to an intramuscular injection of 0·25 mg. β1-24 polypeptide synthetic corticotrophin (Synacthen†) was determined by measuring the plasma cortisol concentration immediately before and 30 minutes after the injection.

*Armour Laboratories Ltd., Hampden Park, Eastbourne.
†Ciba Laboratories Ltd., Horsham, Sussex.

TABLE
RESULTS OF THE PITUITARY ADRENAL FUNCTION TESTS IN 31 PATIENTS IN RELATION TO DOSE OF ACTH AND DURATION OF THERAPY

Case No.	Dose of ACTH	Duration of Therapy (yrs)	"Withdrawal" Cortisol (at 10 a.m.)			ΔCortisol*		
						After Synacthen	After Vasopressin	After Stress
1	40	→14	16·0	19·5	17·0	33·0	22·0	20·0
2	30	8½	6·5	2·5	3·5	23·5	11·5	11·5
3	30	1½	21·5	20·0	18·0	25·0	10·0	17·0
4	26	7	21·5	22·0	8·0	24·0	Nil	32·0
5	22	9/12	25·0	23·0	20·0	12·0	4·0	16·5
6	20	10	23·5	22·5	26·5	21·5	8·0	18·5
7	20	→12	23·0	20·0	31·0	14·0	12·5	24·0
8	20	4/12	19·5	23·5	34·0	35·5	25·5	8·5
9	20	2	28·5	21·5	24·0	22·5	2·0	9·5
10	20	12	22·0	14·5	10·0	20·0	17·5	21·5
11	20	10	30·5	20·0	23·5	25·5	7·5	4·5
12	20	1	21·5	20·0	18·5	27·5	8·0	9·5
13	20	11	28·0	27·0	18·5	25·0	8·0	5·0
14	18	2½	15·5	9·0	13·5	12·5	5·0	19·0
15	18	9	20·5	16·5	22·0	39·5	10·0	26·0
16	16	→10	30·7	9·0	15·0	11·8	12·0	23·5
17	14	9½	11·5	38·5	5·5	41·5	3·0	30·5
18	12	9½	21·0	34·5	16·0	27·0	0·5	16·5
19	10	2	15·5	16·5	24·0	26·5	11·5	21·0
20	8	7½	6·5	7·0	7·5	47·0	6·0	17·0
21	8	2½	28·5	36·5	53·0	48·0	29·5	—11·5
22	6	8	42·5	33·5	29·0	19·0	21·0	23·0
23	6	2½	29·0	16·0	18·0	22·0	11·5	29·0
24	4	1	10·0	17·0	12·0	42·0	27·5	28·5
25	4	7	17·0	21·0	15·0	33·0	21·0	19·5
26	4	3½	34·5	36·5	33·5	44·5	15·0	10·0
27	2	7	13·5	33·0	18·0	26·5	23·0	40·0
28	0	On 9/12 off 1½	18·0	26·0	35·0	41·0	20·5	—17·5
29	0	On 13/12	17·5	12·0	9·0	20·5	30·0	28·0
30	20	2/52						
31	16	1½						

*ΔCortisol is the maximum rise above the baseline observed in each test.

Vasopressin Test

The pituitary-adrenal response to the synthetic octapeptide lysine-8-vasopressin (Vasopressin‡) was determined by measuring the plasma cortisol immediately before and 30 and 60 minutes after the intramuscular injection of 10 pressor units of Vasopressin.

Stress Test

Subjects were stressed with hypoglycaemia, which was induced by the intravenous injection of 0·15 units soluble insulin per kg. body weight. Venous blood samples were withdrawn through an indwelling needle before insulin was injected and every 15 minutes thereafter for glucose and every 30 minutes for cortisol determinations, for a total of 90 minutes.

The above three tests were all performed between 10.00 and 11.30 a.m. on non-fasting out-patients who had omitted their ACTH for 36 hours prior to testing. Patients receiving the stress test were asked to take only a light breakfast on the morning of the test.

Withdrawal Test

Blood was taken for plasma cortisol after temporary withdrawal from ACTH for 36 hours on three separate occasions in each patient. The determinations in this test also formed the initial samples for the three tests described above, but the results are important in themselves and not simply as baseline observations. The duration of action of Acthar Gel in the dosage used is less than 12 hours (Fig. 2); consequently it is reasonable to assume that cortisol in the plasma 36 hours after the injection must have been secreted in response to endogenous corticotrophin.†

Diurnal Rhythm after ACTH Injection

In order to assess whether a single morning plasma cortisol sampled under the conditions of the withdrawal test actually did represent a response to endogenous corticotrophin and was not a residual effect of administered ACTH, plasma cortisol levels were sampled *via* an indwelling needle at frequent intervals throughout the 48 hours following the ACTH injection in seven in-patients. The pattern of the diurnal rhythm of plasma cortisol was thus demonstrated both for the 24 hours after the usual dose of ACTH and for a further 24 hours after the dose had been omitted.

Chemical Estimations

Plasma cortisol was estimated fluorimetrically (Spencer-Peet, Daly, and Smith, 1965). Simple fluorimetric methods measure the small amount of corticosterone present in human plasma as well as cortisol and certain unidentified fluorogens (Daly and Spencer-Peet, 1964). Nevertheless, cortisol is the principal constituent measured (James, Townsend, and Fraser, 1967); therefore the term "plasma cortisol", although not strictly

‡Sandoz Products Ltd., London.

†For the sake of clarity administered adrenocorticotrophin is referred to throughout this paper as ACTH, whilst endogenous adrenocorticotrophin, secreted by the patient, is referred to as corticotrophin.

accurate, is used here for the sake of simplicity. Glucose was determined by a glucose oxidase method (Watson, 1962).

Results

Synacthen Test

The mean rise in plasma cortisol after Synacthen was 28·0 μg./100 ml. (range 12·0-47·0) (Fig. 1) compared with a mean rise of 19·4 (range 10-30) seen in a control group of eighteen rheumatoid arthritics who had not received ACTH or corticosteroids. Wood, Frankland, James, and Landon (1965) found a mean rise of 16·7 μg./100 ml. (range 7·5-27·5) in normal subjects, and in cases of arthritis who had not received corticosteroids or ACTH Greig, Browning, Boyle, and Maxwell (1966) found the mean rise to be 16·3 μg./100 ml.

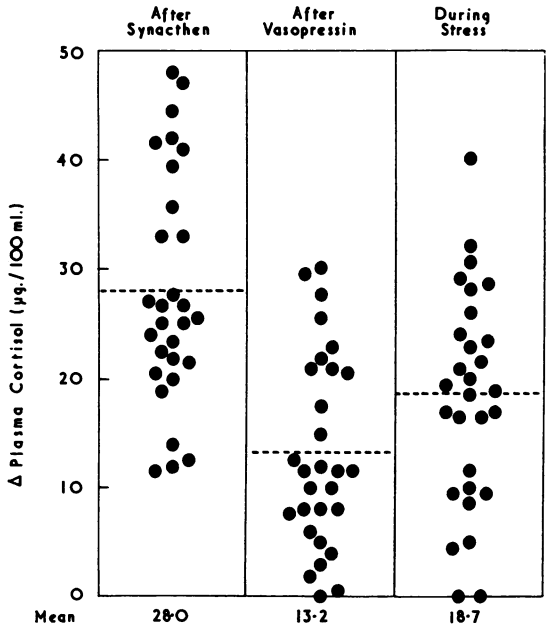

Fig. 1.—Maximum rise in plasma cortisol (Δ) observed during pituitary-adrenal function tests.

The marked increase in adrenal responsiveness seen in our patients agrees with the increased response to ACTH infusion reported by Reed, Clayman, and Palmer (1964) in patients treated with prolonged ACTH, and is compatible with the hypertrophy of the adrenal glands induced by such treatment (O'Donnell, Fajans, and Weinbaum, 1951). By contrast, Nelson and others (1966) showed that patients who have received ACTH only once, twice, or thrice weekly do not show an enhanced response to Synacthen. These workers found a mean rise in the plasma cortisol of only 15·0 μg./100 ml. after Synacthen, but they noted that the greatest responses occurred in those receiving the most frequent doses of ACTH.

The magnitude of the Synacthen response in our study bore no relationship to the duration of ACTH therapy, and increased responses to Synacthen were seen in some patients who had been receiving ACTH for less than one year. No correlation could be seen between the dose at the time of testing and the response to Synacthen.

Vasopressin Test

The mean maximum rise in plasma cortisol after Vasopressin was 13·2 μg./100 ml. (range 0-30) (Fig. 1). This compares closely to the mean of 13·8 found in a control group of ten arthritics who had not received corticosteroids or ACTH. Nelson and others (1966) also found a mean rise of 13·8 μg./100 ml. in control subjects. In view of the adrenal hyper-responsiveness to Synacthen shown in our patients, this may indicate a release of endogenous corticotrophin in response to Vasopressin which is less than normal. Two patients (Cases 4 and 18) showed no response. Nelson and others noted a reduced response to Vasopressin in patients on intermittent ACTH who did not have increased response to Synacthen. Four of their patients and two of their controls failed to show any response to Vasopressin. Sussman, Librik, and Clayton (1965) also noted impaired responsiveness to Vasopressin in normal subjects after 3 days on a high dosage of ACTH.

The magnitude of the response to Vasopressin in this study bore no relationship to either the current dose of ACTH or to the total duration of therapy.

Stress Test

The mean maximum rise in plasma cortisol during the stress test was 18·7 μg./100 ml. (Fig. 1), which is a little higher than the means of 12·8 μg./100 ml. reported in twelve control subjects by Landon, Wynn, and James (1963) and 15·4 μg./100 ml. reported in 28 subjects by Greenwood, Landon, and Stamp (1966).

The mean rise is less than the mean rise in the Synacthen test, but all except four subjects (Cases 11, 13, 21, and 28) had a rise of more than 7·8 μg./100 ml., the minimum normal rise found by Greenwood and others (1966). Two of these (Cases 21 and 28) failed to show any response at all despite apparently adequate hypoglycaemia. Both started with a very high baseline plasma cortisol, the highest in this series, and the level fell steadily throughout the test.

The high initial level suggests that both these patients may have been already "stressed" before they received insulin, although there was no obvious cause for this. This may explain their failure to show any additional rise during the test. Cases 11 and 13 also showed a poor response, but did not start from so high a baseline.

There is no correlation between either the duration of ACTH therapy or the dose at the time of testing and the degree of response to stress.

Withdrawal Test

The mean level of plasma cortisol in the morning after withdrawal of ACTH was 21·5 μg./100 ml. (range 2·5-53·0). This compares with a mean of 12·4 μg./100 ml. (range 4-34) found at the same time of day in normal controls in this department. This high level of plasma cortisol after ACTH withdrawal suggests that the hypertrophied adrenal in these subjects may be hypersensitive to normal amounts of endogenous corticotrophin. The alternative explanation of an increased release of corticotrophin in response to withdrawal is less likely in view of the results of the Vasopressin test. Also it has been shown that ACTH administration inhibits endogenous corticotrophin release in rats (Kitay, Holub, and Jailer, 1959).

A wide range of plasma cortisol levels is seen in this test but once again this shows no relationship to the duration of therapy or to the current dose.

Several patients also showed a wide scatter in the three results obtained, but only one patient had a plasma cortisol that was persistently at or below the lower limit of normal.

Diurnal Rhythms after ACTH

In five patients the plasma cortisol level was studied for 48 hours after their last dose of ACTH. Two other patients were less fully studied, one being followed for the first 24 hours after ACTH only and the other for the 24 to 48 hour period only.

The results (Fig. 2) demonstrate a rapid rise in plasma cortisol after the injection of ACTH to levels well above the normal range. The levels continued to rise for 4 to 7 hours and thereafter fell steadily, showing that the duration of action of ACTH is relatively brief. The fall continued for about 24 hours, after which the plasma cortisol level rose again. This confirms that the normal or high plasma cortisol noted in the morning in the withdrawal test is not the tail-end of the response to administered ACTH but represents a spontaneous rise. The pattern of the plasma cortisol in the second 24 hours is an early morning rise followed by a fall later in the day, very similar to the pattern seen in normal subjects. All the patients tested had reverted to a normal diurnal rhythm on the day immediately after ACTH was omitted. It is notable that after the ACTH peak the plasma cortisol fell to low levels by the following evening. This low level may act as the stimulus to endogenous corticotrophin release which triggers off the normal diurnal variation on the following day.

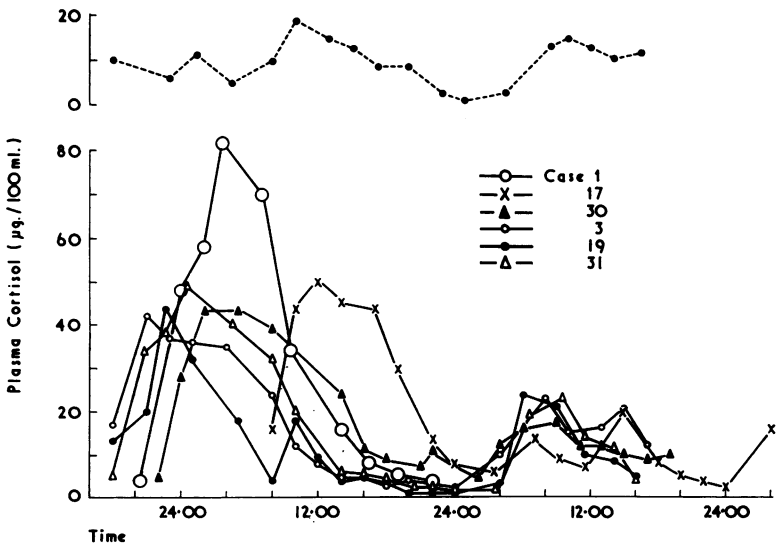

Fig. 2.—Diurnal rhythm in plasma cortisol followed for up to 48 hours after a single dose of ACTH. The first point on each graph corresponds to the time at which ACTH was given. The upper graph, representing the diurnal rhythm in a patient who had not received ACTH or corticosteroids, is shown for comparison.

Discussion

The particular combination of tests was chosen in an attempt to assess the responsiveness of the hypothalamo-pituitary-adrenal axis at several levels.

Synacthen tests the ability of the adrenal to respond to ACTH. Vasopressin is believed to mimic the action of the neurohormone, corticotrophin releasing factor (CRF), and thus tests the ability of the anterior pituitary to release corticotrophin in response to CRF (Landon, James, and Stoker, 1965; Gwinup, 1965). Hypoglycaemia acts as a stress to which the hypothalamus should respond by secreting CRF. Finally, the withdrawal test is a measure of the integrity of the feedback response to a low plasma cortisol produced by sudden omission of the stimulus of administered ACTH. If a normal plasma cortisol is maintained or promptly restored despite such withdrawal, endogenous corticotrophin production must be occurring.

The withdrawal test is perhaps the most important of all the functional tests carried out, as it has immediate clinical relevance. It indicates the patient's ability to resume production of cortisol without exogenous adrenal stimulation, and is thus a test of the functional integrity of the entire HPA axis. It is more relevant than artificial tests which are stated, largely on the basis of animal experiments, to act at specified levels of the axis but whose precise mode and site of action are not always certain in man. This uncertainty applies particularly to the Vasopressin test, the results of which did not correlate well with the results of the other tests in this study. Thus seven subjects showed a rise of less than 7 μg./100 ml. after Vasopressin, yet made good responses to stress. This appears incompatible with the mode of action of Vasopressin postulated above.

The results of this study reveal no tendency for suppression of the HPA axis to occur either with increasing dose, within the range used, or with increasing duration of therapy. The mean response to each test shows no depression below the normal levels reported in the literature and no individual showed an abnormal response to more than one test. The four patients who showed an impaired response to stress all showed a normal plasma cortisol in the withdrawal test, whilst the one patient who made a consistently low response to withdrawal showed a good response to stress. This contrasts with the results of a similar study on a group of corticosteroid-treated rheumatoid arthritics, in whom nearly one-third showed evidence of suppression of the HPA axis (Daly, Myles, Bacon, Beardwell, and Savage, 1967).

We have considered three main possible explanations for the apparent failure of long-term ACTH to suppress the HPA axis in our patients.

(1) In contrast to the established negative feedback system activated by cortisol, it is possible that no physiological mechanism exists whereby a high circulating corticotrophin level causes acute inhibition of further production of the hormone. However, this is considered to be unlikely for several reasons. It has been shown experimentally that ACTH as well as corticosteroids can activate the negative feedback system in rats (Motta, Mangili, and Martini, 1965; Vernikos-Danellis and Trigg, 1967). Even if there is no ACTH feedback in man, the high cortisol levels produced by ACTH might be expected to lead to HPA suppression in exactly the same way as exogenously-administered corticosteroids. Indeed, in humans treated with ACTH, Crooke's hyaline change has been noted in the basophil cells of the pituitary as in corticosteroid-treated patients (Kilby, Bennett, and Sprague, 1957).

(2) It is possible that the dose of ACTH used in our patients was too small to produce acute HPA suppression but it seems unlikely that this could be the entire reason. The dosage was sufficient to produce a considerable increase in the mean response to Synacthen, and a marked rise in the plasma cortisol above the normal range was seen after the injection of ACTH in those patients whose diurnal rhythm was followed. A good clinical response was seen in all the patients in this group and in addition 20 of the patients showed Cushingoid changes at some time. Finally, there was no difference in the test results between patients in the upper and lower levels of the dose range used.

(3) The use of a single daily dose of ACTH may be the most important explanation for the lack of HPA suppression. The results of our investigation into the diurnal rhythm demonstrate that the plasma cortisol has fallen to a low level well within 24 hours. Thus, from the beginning of ACTH treatment, there have been several hours each day when the patient's HPA axis is not being suppressed by either a high circulating ACTH or a raised plasma cortisol level. Nelson and others (1966) found a normally functioning HPA axis in patients given ACTH one to three times a week. They considered this was due to the intermittancy of the therapy. We agree with this, but it appears that the dose does not have to be so widely spaced as they suggest. In the dose range used in these patients an interval of 24 hours between doses is sufficient to avoid suppression.

The results of this study have shown that there is little evidence of HPA suppression following long term therapy with a single moderate daily dose of ACTH. Similarly, Friedman and Stimmler (1966) showed that there was no inhibition of the growth hormone response to hypoglycaemia in patients receiving ACTH therapy in contrast to the findings of Hartog, Gaafar, and Fraser (1964) and Frantz and Rabkin (1964), who found suppression of this response in corticosteroid treated patients. Thus ACTH, although it shares many side effects with oral corticosteroids and produces an unexplained depression of the response to vasopressin, appears to have less risk of producing iatrogenic hypopituitarism. This is an important consideration when treating patients such as rheumatoid arthritics for whom long-term therapy may be indicated.

Summary

31 patients with rheumatoid arthritis who had been treated with a single daily injection of ACTH for from 1 to 14 years were investigated. The integrity of their hypothalamo-pituitary-adrenal (HPA) axis, using the Synacthen, Vasopressin, and insulin-hypoglycaemia tests, and their response to acute withdrawal of ACTH were assessed. The group as a whole showed an increased adrenal responsiveness to Synacthen compared to the normal but an apparently diminished response to Vasopressin. The ability to produce a normal plasma cortisol in the withdrawal tests shown by all except one patient together with the normal response to stress seen in the majority indicates that there is less risk of severe HPA suppression after long-term ACTH therapy than after oral corticosteroids. We suggest that this may be due to the intermittent nature of the adrenal stimulation which is provided by a single daily dose of ACTH, as demonstrated by the studies of diurnal variation of cortisol in these patients.

One of the authors (J.R.D.) gratefully acknowledges the assistance of a grant from Syntex Pharmaceuticals Ltd., Maidenhead, England. We are grateful to Mr J. Hawthorne, Mrs M. Rake, and Miss B. O'Riordain for skilled technical assistance, to Sandoz Ltd. who supplied the Vasopressin, to the Armour Laboratories for help with supplies of ACTH, and to Ciba Laboratories for supplies of Synacthen.

This work was aided by grants from the Ministry of Health and the Arthritis and Rheumatism Council.

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Fonction hypothalamo-pituito-surrénalienne chez des malades soumis à un traitement prolongé par l'adrénocorticotrophine

RÉSUMÉ

On étudia 31 malades atteints de polyarthrite rhumatoïde et traités par une seule injection quotidienne d'ACTH pendant des périodes allant de 1 à 14 ans. On détermina l'intégrité de l'axe hypothalamo-pituito-surrénalien (HPA) en utilisant les tests au Synacthène, à la vasopressine et celui de l'hypoglycémie induite par l'insuline. Dans l'ensemble le groupe accusa une sensibilité surrénale accrue au Synacthène, comparée à celle des témoins, mais apparemment la réponse à la vasopressine fut diminuée. La capacité de produire du cortisol plasmatique normal lors de l'épreuve de sevrage mise en évidence chez tous les malades sauf un, ainsi que la réponse normale au stress observée chez la majorité d'entre eux, montre que le risque d'une dépression grave de l'axe HPA est moindre après une thérapeutique prolongée par l'ACTH que par celle des corticostéroïdes administrés par voie orale. Nous suggérons que ceci peut être dû à l'intermittence de la stimulation surrénale, provoquée par une seule dose quotidienne d'ACTH, comme l'ont montré les études des variations diurnes du cortisol chez ces malades.

La función hipotalamo-pituito-suprarrenal en enfermos sometidos a un tratamiento prolongado con corticotropina

SUMARIO

Se estudiaron 31 enfermos con artritis reumatoide tratados con una inyección diaria de ACTH durante periodos de uno a 14 años. Se determinó la integridad del eje hipotálamo-pituito-suprarrenal (HPA) mediante los tests de Synacthen, de vasopresina y de hipoglicemia inducida por la insulina. El grupo en su enteridad acusó una sensibilidad suprarrenal aumentada con Synacthen en comparación con la normal pero una respuesta aparentemente dismunuida a la vasopresina. La capacidad para producir cortisol plasmático normal en pruebas de supresión medicamentosa, evidenciada en todos los enfermo salvo uno, así como la respuesta normal al stress observada en la mayoría de ellos, mustra que el riesgo de una depresión grave del eje HPA es menor con el tratamiento prolongado con la corticotropina que con la terapia con corticosteroides por vía oral. Se sugiere que esto puede deberse a la naturaleza intermitente de la estimulación suprarrenal ofrecida por una sola dosis diaria de ACTH, cual hecho fué confirmado por los estudios de las variaciones diurnas del cortisol en estos enfermos.