PLASMA "CORTISOL" RESPONSE TO SYNACTHEN IN PATIENTS ON LONG-TERM SMALL-DOSE PREDNISONE THERAPY

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In view of the uncertainty about safe limits of steroid dosage and of the particular interest in the 5 mg. per day dose level (de Andrade, McCormick, and Hill, 1964), we studied adrenal cortical responsiveness in a series of patients with rheumatoid arthritis, who had been on this dose of prednisone for varying periods, by the Synacthen test (Wood, Frankland, James, and Landon, 1965).

Material

Patients.—39 patients were studied, all but one of whom had taken prednisone 5 mg./day for periods of from 8 weeks to 8 years. One patient (Case 31) had her dose increased from 5 to 7 mg./day 8 months before the test. With the exception of two who had polymyalgia rheumatica, all had rheumatoid arthritis. Of these 39 patients, nineteen were selected at random and studied again after a year to discover the effects of continued or altered prednisone dosage upon adrenal function.

Control.—Twenty normal hospitalized controls of comparable age range were studied under the same test conditions as the patients.

Methods

Plasma "cortisol" was estimated by a modification of the technique of Mattingly (1962) for free 11-hydroxy-corticoids. In this technique both cortisol and corticosterone are measured. The amounts of circulating corticosterone are small and since the present study is essentially comparative, the result is referred to as plasma "cortisol". Prednisone does not interfere with the estimated result by more than 1 per cent.

Synacthen Test.—All tests were carried out on non-fasting subjects starting between 9 and 10 a.m. None of the patients had taken any steroid for at least 12 hours before the test. Between 9 and 10 a.m. samples of venous blood were collected for the estimation of resting levels of plasma cortisol. 250 μ g. Synacthen in 0.5 ml. sterile water were then injected intramuscularly. A sample of blood was collected at 30 and 60 minutes after the injection of Synacthen. The 60-minute samples were

estimated in all cases. Although these latter values are not given in the Tables of results they were used to confirm the 30-minute values in order to exclude the possibility of a delay in absorption as being the cause of an abnormal response.

Results

In the twenty normal control subjects, the resting level of plasma "cortisol" at 9 a.m. varied between 7.0 and 22.7 μ g./100 ml. (mean 14.9 μ g.); 30 minutes after the injection of Synacthen values varied between 25.5 and 36.5 μ g./100 ml. (mean 31 μ g.). Our criteria for a normal Synacthen test were the finding of both:

- (1) A baseline plasma "cortisol" value of 7 μ g./100 ml. or more.
- (2) An increment at 30 minutes of 10 μ g./100 ml. or more on the baseline value.

These criteria are in accordance with those of other workers (Wood and others, 1965; Greig, Browning, Boyle, and Maxwell, 1966).

Table I (overleaf) shows the results in 39 patients, whose total dose of steroid varied from 0.3 to 14.2 g. prednisone, and whose period of treatment varied from 8 weeks to 8 years. They are arranged in order of total dosage which corresponds closely to the number of weeks of treatment.

No patient was found to have evidence of lack of adrenal responsiveness during the first year of treatment, but Case 21 showed an abnormal response at one year. This patient had been previously treated with steroids at another hospital, but had been on 5 mg./day for 52 weeks at this hospital. The other three patients (Cases 31, 37, 39) with a lack of adrenal response had all received large doses of steroid. Three patients (Cases 6, 16, 22) showed low baseline values but a normal increment after the Synacthen, whereas six others (Cases 1, 8, 20, 25, 26, 34) with normal baseline

TABLE I
ADRENAL RESPONSES OF PATIENTS ON SMALL DOSES OF PREDNISONE

Patient No.	Total Dose (mg.)	Total No. of Weeks	Plasma Control		
			Resting	30' after Synacthen	Differences
1	280	8	20	26*	6*
2	350	10	14	44	30
3	385	11	9	35	26
4	455	13	16	33	17
5	490	14	16	28	14
6	525	15	19	33	14
7	545	15	9	22	13
8	560	16	17	25*	8*
9	630	18	12	25	13
10	665	17	8	20	12
11	700	20	16	28	12
12	770	22	13	29	16
13	875	21	15	32	17
14	1015	29	17	39	22
15	1050	30	20	50	30
16	1050	30	8	23	15
17	1435	37	10	22	12
18	1635	46	10	20	10
19	1645	47	15	26	11
20	1680	48	23	32*	9*
21	1820	52	6*	13	7*
22	1855	53	5*	15	10
23	1995	57	10	25	15
24	2105	64	24	35	11
25	2240	59	27	36*	9*
26	2240	64	15	23*	8*
27	2275	62	18	21	3*
28	2380	68	10	22	12
29	2430	70	14	29	15
30	2490	105	25	38	13
31	2555	71	6*	14*	8*
32	2575	74	6*	21	15
33	2887	94	14	27	13
34	2995	86	15	24*	9*
35	3255	93	14	27	13
36	3650	104	4*	19	15
37	6600	188	2*	8*	6*
38	7300	203	16	31	15
39	14225	406	8	12*	4*

*Indicates abnormal value. Patients with adrenal suppression in **bold** type.

values showed a subnormal increment after Synacthen after variable doses of steroids. The four patients with clear evidence of lack of adrenal response (21, 31, 37, 39) are scattered in a random fashion in the Table, suggesting that individual variation in sensitivity to the 5 mg. dose is of more importance than total dose or total time. The plasma "cortisol" at 60 minutes in these four patients was still poor, suggesting that poor absorption of Synacthen was not the basis of their poor response.

Table IIA compares the results of the first and second tests after one year, on ten patients who remained on the same dose of prednisone. Two (34 and 35) showed an increased resting level and increment after Synacthen despite a further 76 and 44 weeks treatment respectively. The other eight patients showed a decrease in either the baseline plasma "cortisol" level or the increment after Synacthen. One previously abnormal patient (21) remained abnormal, and one further patient (32) who had previously shown a normal response became abnormal; the latter had an abnormal low

baseline level at the first test. Two patients (22 and 23), although showing a normal increment after Synacthen, showed low baseline values after further steroid therapy.

Table IIB compares the results of first and second tests of five patients whose dose was in some way reduced between the first and second tests. One patient (39), who had had the largest amount of steroid of all, became normal on reducing the daily dose from 5 to 4 mg./day. In contrast, patient 8, in whom the steroid had been reduced to 4 mg./day for several months after a relatively small total initial dose, had become abnormal by the time of the second test. Patient 37 remained abnormal despite a reduction in the daily dose of steroid from 7 to 5 mg. prednisone.

Table IIC shows that three patients whose prednisone was stopped between the first and second tests all had normal tests on the second occasion, including one (31) who had an abnormal response previously.

Table IID shows that, in one patient whose dose was increased (29), the test on the second occasion was markedly abnormal.

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TABLE II
RESULTS OF REPEAT SYNACTHEN TESTS

Group	Patient No.	First Test					Second Test					Notes
		Total Dose	Total Time	Plasma "Cortisol" (μg./100 ml.)			Total Dose	Total Time	Plasma "Cortisol" (μg./100 ml.)			
				Resting	30'	Increment			Resting	30'	Increment	
(A) Same Dose	3	385	11	9	35	26	3080	88	21	37	16	
	14	1015	29	17	39	22	3710	105	20	44	24	
	19	1045	47	15	26	11	4235	121	8	20	12	
	21	1820	52	6*	13*	7*	4340	124	4*	12*	8*	
	22	1855	53	5*	15	10	3220	93	5*	17	12	
	23	1995	57	10	25	15	4410	126	1*	14	13	
	28	2380	68	10	22	12	3990	114	12	20*	8*	
	32	2575	74	6*	21	15	4955	146	5*	14*	9*	
	34	2995	86	15	24*	9*	4535	130	19	34	15	
	35	3255	93	14	27	13	4830	138	17	28	11	
(B) Dose Reduced	8	560	16	17	25*	8*	2627	89	5*	11*	6*	Adjustments in Dosage: Reduced to 4 mg. then back to 5 mg./day Reduced to 2 mg./day during last 2 months Reduced to 3 mg./day Reduced from 7 to 5 mg./day Reduced to 4 mg./day
	26	2240	64	15	23*	8*	4200	137	13	25	12	
	33	2881	94	14	27	13	4148	139	8	21	13	
	37	6600	188	2*	8*	6*	9813	273	3*	6*	3*	
	39	14,227	406	8*	12*	4*	16,577	490	8	19	11	
(C) Dose Discontinued	18	1635	46	10	20	10	2958	91	13	37	24	
	31	2535	71	6*	14*	8*	3306	95	14	33	19	
	38	7300	208	16	31	15	9197	313	18	32	14	
(D) Dose Increased	29	2430	70	14	29	15	5895	144	1*	8*	7*	Steroid increased from 5 to 10 mg./day

*Indicates abnormal value. Patients with adrenal suppression in **bold** type.

Discussion

It has been suggested that there is a relationship between the incidence of adrenal cortical suppression and the dose and duration of treatment of steroid therapy (Savage, 1966; de Andrade and others, 1964), but this relationship is not universally confirmed (Livanou, Ferriman, and James, 1965). The differing numerical values that have been suggested as safe limits of prednisone dosage are shown in Table III. These figures imply that the product of the dose given multiplied by the duration of treatment can be used to calculate either a safe total dose or a safe duration of treatment.

TABLE III
SUGGESTED SAFE LIMITS OF PREDNISONE DOSAGE

Reference	Total Dose (g.)	Total Time
Treadwell and others 1963	4.6	30 mths at 7 mg./day
Jørgensen 1965	5.8	
Goth, Görgényi, Fövényi, and Szántó 1964	3	10 yrs at 5 mg./day
Hamaty 1966	18.2	

5 mg. prednisone is the equivalent of the daily adrenal glucocorticoid output (Peterson and Wyn-gaarden, 1956). Shuster and Williams (1961) found

no evidence that 5 mg. exogenous prednisone suppressed endogenous cortisol production during the period they studied. Jørgensen (1965) found no abnormality in the ACTH response until a total dose of 5.8 mg. prednisone had been given. Hamaty (1966) suggested that 18.2 g. prednisone could be tolerated as 5 mg./day for 10 years. In contrast Goth, Görgényi, Fövényi, and Szántó (1964) found abnormalities to the ACTH test developing between a total dose 1 and 2 g. of prednisone.

These earlier series consist of patients on a variety of doses for a variety of times. It is therefore necessary, in using their results, to predict the progress of adrenal suppression in other patients, to assume that the figure given by multiplying the total dose by the total time can be applied equally to calculate a safe total dose or time in another patient. There is very little evidence to support this. It may well be that 5 mg./day can be tolerated for much longer than twice the time which the same patient can tolerate 10 mg./day, and very probably for much longer than four times the same patient's endurance at 20 mg./day.

Therefore the kind of study reported here, in which the patients are all taking the same daily dose for various times, is more likely to produce a clear picture of at least a segment of what may be a three

dimensional graph. The study shows that the daily dose of 5 mg./day prednisone is not free of the danger of adrenal suppression; moreover, even from a study concentrated on only one aspect of the time/dose relationship, it is not possible to predict the onset of adrenal suppression. Individual testing is therefore necessary. The results from those patients whose adrenal function was tested on a second occasion suggest that, while the onset of adrenal suppression is so greatly influenced by the individual sensitivity as to appear random, the progress of each patient's adrenal function seems to follow simple pharmacological concepts, tending to deteriorate where prednisone is continued at the same daily level or increased, and tending to improve where the daily dose is adequately reduced or discontinued.

Summary

39 patients on prolonged low doses of steroids were studied by the Synacthen test for evidence of adrenal suppression. Four had unequivocally

abnormal tests. No abnormality occurred before the end of one year, but thereafter there was no relationship between total dose, total time, and onset of suppression.

Nineteen of the patients were re-tested after an interval of one year to assess the effects of altered continued steroid therapy.

The dose level of 5 mg./day prednisone is not free of the danger of adrenal suppression. The variation in individual sensitivity is so great that predictions cannot be made, and each patient must be treated separately. Adrenal function proceeds as might be expected from a simple dose-response relationship when studied over a period of time, but individual variability is still evident.

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La réponse du cortisol plasmatique au Synacthène chez des malades traités longtemps par de petites doses de prednisone**RÉSUMÉ**

Chez 39 malades soumis à un traitement prolongé par de petites doses de stéroïdes on rechercha des signes de dépression de la fonction surrénale par le test au Synacthène. Chez quatre malades les résultats de ce test furent indubitablement anormaux. Aucune anomalie n'apparût avant la fin de la première année, mais après cela il n'y eut pas de relation entre la dose totale, la durée totale et le début de la dépression.

On répéta le test après un intervalle d'un an chez 19 malades pour déterminer les effets du traitement stéroïdien modifié ou non.

La dose quotidienne de 5 mg. de prednisone n'est pas exempte du danger de dépression surrénale. La variation de la sensibilité individuelle est si grande que des prédictions ne peuvent pas être faites, et que chaque malade doit être traité comme un cas particulier. La fonction surrénale suit son cours prévu, compte tenu simplement de la relation entre dose et réponse pendant une certaine période, mais la labilité individuelle est encore présente.

La respuesta del cortisol plasmático al Synacthen en enfermos tratados durante un tiempo prolongado con dosis pequeñas de prednisona**SUMARIO**

En 39 enfermos sometidos a un tratamiento prolongado con pequeñas dosis de esteroides se buscaron pruebas de depresión de la función suprarrenal por el test de Synacthen. En cuatro enfermos los resultados de este test fueron inequívocamente anormales. No anomalías ocurrieron durante el primer año del tratamiento, pero a partir del segundo año no hubo relación alguna entre la dosis total, la duración total y el principio de la depresión.

En 19 enfermos el test fué repetido después de un intervalo de un año para determinar los efectos del tratamiento esteroide continuo o alterado.

La dosis diaria de 5 mg. de prednisona no se ve exenta del peligro de depresión suprarrenal. La variación de la sensibilidad individual es tal que el resultado no se puede anticipar y cada paciente debe tratarse separadamente. La función suprarrenal sigue un curso que se puede prever al estudiar la simple relación entre la dosis y la respuesta durante un período de tiempo, pero la variabilidad individual queda en evidencia.