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COMPARISON OF
PITUITARY-ADRENOCORTICAL FUNCTION
IN ASTHMATIC PATIENTS GIVEN
LONG-TERM CORTICOSTEROID THERAPY AND
IN ASTHMATICS WHO HAVE NOT RECEIVED
ADRENAL STEROIDS

By

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The suppression of pituitary-adrenal function following prolonged administration of adrenal steroid therapy is well known and has frequently been described also in asthmatic patients. Although the mechanism of the suppression of the endogenous hormone production has not been completely elucidated most recent investigations would seem to indicate that the suppressive effect of the long-term corticosteroid treatment is mainly directed at the pituitary level or some hypothalamic site concerned with the production of corticotrophin releasing factors and that adrenocortical failure in most cases must be regarded as a secondary effect of the suppression of endogenous ACTH production (*Carreon et al.* 1960, *Andersson & Kjerulf* 1961, *Graber et al.* 1965, *Jørgensen* 1965, *Arnoldsson* 1967).

We have recently investigated this problem in asthmatic patients and in patients with rheumatoid arthritis who had received long-term adrenal steroid therapy (*Jakobson et al.* 1968). The pituitary ACTH-response was during the course of the study evaluated by determining the increment in the

excretion of urinary 11-deoxy-17-hydroxycorticosteroids during the oral administration of metyrapone and the adrenal response to ACTH by the excretion of 11-oxygenated corticosteroids.

The metyrapone responses were in the steroid-treated patients frequently found to be more reduced after comparatively smaller doses of corticosteroids than the adrenal responses to ACTH observed in the same patients, which is compatible with the above mentioned view concerning the mechanism of the suppressive effect of long-term glucocorticoid therapy. The suppression of the endogenous hormone production was, however, during the study found to be more marked in the asthmatic patients than in the patients with rheumatoid arthritis who had received comparable doses of adrenal steroids during similar periods.

A possible explanation for the difference observed between the two groups of patients could perhaps be found in the evidence of decreased adrenocortical function which by some early investigators has been observed in patients with continuous asthma who have not been treated with corticosteroids (*Eriksson-Lihr et al.* 1949, *Eriksson-Lihr* 1951, *Andersson* 1953, *Rose et al.* 1955) and has also been claimed on the basis of a few more recent reports (*Vaccarezza* 1961, *Robson & Kilborn* 1965). Because conflicting evidence has been presented by other workers it was thought worthwhile to compare pituitary-adrenal function in patients with severe bronchial asthma receiving long-term adrenal steroid therapy and in asthmatic subjects who have not received adrenal steroids.

MATERIAL AND METHODS

Pituitary-adrenal function was determined in 48 asthmatic patients of whom 20 had received long-term treatment with adrenal steroids and 28 had not received corticosteroids. The duration of continuous steroid treatment in the former group of patients ranged from $\frac{1}{2}$ to 10 years (mean 3.1 years) except in two patients who had received corticosteroids intermittently. The drugs used were prednisolone (in 9 patients), prednisone (2), triamcinolone (6), dexamethasone (2) and betamethasone-[flubenzinolone] (1). The steroids were ad-

ministered in divided doses in 14 patients and in the form of one daily dose in 6 cases. The daily dose varied from 5 to 20 mg of prednisolone or its equivalent. The total administered dose of adrenal steroids was calculated by multiplying the daily dose by the duration of treatment and expressed as the equivalent amount of prednisolone (5 mg of prednisolone or prednisone = 4 mg of triamcinolone = 0.75 mg dexamethasone = 0.5 mg betamethasone). It ranged from 1.8 to 36 g of prednisolone. The known duration of the disease was recorded in all cases and the patients were in addition according to the severity of the asthmatic condition divided into three clinical categories. The patients who were receiving adrenal steroid therapy belonged with the exception of one case to the group of patients with the severest degree of asthma (3°). Determinations of urinary 17-hydroxycorticoids (17-OHCS) were in all patients performed in the laboratory of the Hospital for Allergic diseases by the procedure of *Appleby et al.* (1955). The method was modified according to *Kraushaar et al.* (1966) and *Vestergaard & Sayegh* (1966) periodate being used instead of bismuthate for the oxidation of the conjugated steroids. Normal values obtained with this method ranged in men from 7.5 to 16.0 mg/24 hrs (Mean 8.2 mg/24 hrs) and in women from 5.0 to 14.0 mg/24 hrs (Mean 6.2 mg/24 hrs.).

The mean of two determinations performed on consecutive days was used as a measure of the basal excretion of urinary 17-OHCS. Metyrapone was thereafter administered orally in a dose of 750 mg given four-hourly for 24 or 48 hours and the maximal increase of urinary 17-OHCS on either of these two days or on the next day was used as a measure of the ACTH-secretion capacity of the pituitary in response to the blocking agent. The metyrapone response was regarded as subnormal if the increase in the excretion of urinary 17-OHCS amounted to less than twice the basal excretion level. The ACTH-test was performed two days later by administering 75 IU of a water-soluble ACTH preparation in 500 ml of physiological saline over a 6-hour period. The increase of the urinary excretion of 17-OHCS during the 24-hour period during which the intravenous infusion of ACTH was carried out was used as a measure of adrenal responsiveness to ACTH and a rise to two or three times the basal value was considered adequate. The administration of adrenal steroids was in the steroid-treated asthmatics discontinued two or three days prior to the performance of the pituitary-adrenal function tests except in six patients who received 0.5 to 1.0 mg of dexamethasone during the tests. Dexamethasone in these doses does not interfere with the methods used for the determination of urinary corticoids. No withdrawal symptoms worth mentioning were seen in the patients who had previously received adrenal steroids and no adverse reactions were observed during the metyrapone tests except for slight nausea or other signs of gastrointestinal irritation which in a few cases were observed following the administration of the blocking agent.

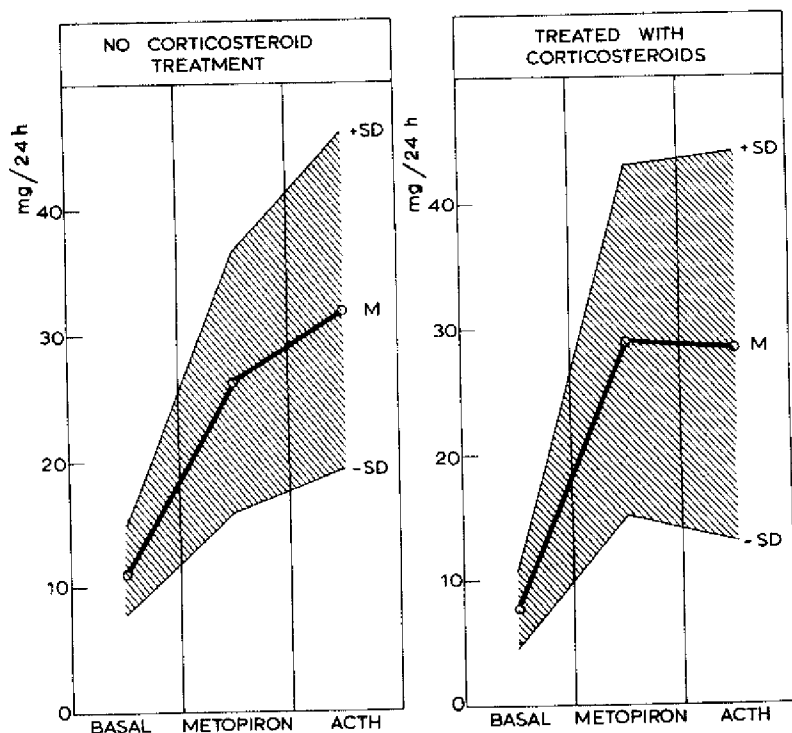


Fig. 1.

Excretion of Urinary 17-hydroxycorticoids in Corticosteroid-treated Asthmatic Patients and in Asthmatics who have not received Corticosteroid.

Mean values for the basal 17-OHCS excretion and the response of the urinary corticoids to the administration of metyrapone (Metopiron) or ACTH are indicated by open circles and the shaded area represents the standard deviation. Metyrapone was in the corticosteroid-treated patients administered for two days and in the other asthmatic patients for one day.

RESULTS

Fig. 1 shows the basal excretion of urinary 17-OHCS and the response of the urinary corticoid excretion to the administration of metyrapone or to the intravenous administration of ACTH in steroid-treated asthmatic patients and in the group of asthmatics who have not received adrenal steroid therapy. The mean basal excretion of urinary steroids and

the response to ACTH were both less pronounced in the asthmatic patients who had received long-term treatment with adrenal steroids than in the control group the difference in the basal excretion of urinary 17-OHCS between the two groups being statistically significant ($p < 0.001$). The metyrapone response obtained in the steroid-treated patients in whom the blocking agent was administered for two days was of a similar magnitude as in the other asthmatics in whom the metyrapone test was carried out during one day only.

The basal excretion of urinary 17-OHCS of individual steroid-treated asthmatic patients; the results of the metyrapone- and ACTH-tests, the duration of the disease and the total administered dose of adrenal steroids expressed as the equivalent amount of prednisolone are shown in Table 1. All patients included in this group had severe bronchial asthma of so-called endogenous type and had received adrenal steroids continuously except for two patients (subjects No. 3 and 6) in whom the steroid therapy had been administered intermittently. For the determination of the metyrapone response urinary 17-OHCS excretion was measured on each of the two days during which the blocking agent was administered and during the next day and the highest value for the three days was used as a measure of the pituitary ACTH secretion capacity.

An increase of the urinary excretion of 17-OHCS to less than twice the basal value was during the administration of metyrapone observed in six patients (subjects No. 1, 3, 4, 5, 6 and 9) of whom four (subjects No. 4, 5, 6 and 9) showed at the same time a definitively subnormal ACTH response. A subnormal basal excretion of urinary 17-OHCS consisting of less than 5 mg/24 hrs was observed in two additional patients (subjects No. 10 and 18). The duration of asthma and/or the total administered dose of adrenal steroids was in most of these patients above the mean values of the group shown at the bottom of the table.

The basal excretion of urinary 17-OHCS was not found to be increased in any case while hyperreactive metyrapone and/

TABLE 1

Details of Patients and Results of Urinary 17-OHCS Determinations in Steroid-Treated Asthmatics During Basal Conditions and Following the Administration of Metyrapone or ACTH.

Subject	Age/Sex	Duration of disease (years)	Type of adrenal steroid administered	Total administered dose of steroids (g of Prednisolone or equivalent)	Urinary 17-OHCS mg/24 hours		
					Basal excretion	Response to metyrapone (750 mg q. 4 hrs. for 48 hrs.)	Response to i.v. ACTH
1	62/F	9	Prednisolone	10.8	5.9	11.2	16.8
2	59/F	6	Prednisolone	7.2	11.7	25.2	22.8
3	43/M	2	Dexamethasone	—	8.9	13.3	24.8
4	52/F	8	Prednisolone	14.4	4.8	8.8	8.8
5	53/F	42	Prednisolone	1.8	5.4	9.8	8.6
6	41/F	18	Prednisolone	—	8.0	12.4	10.0
7	40/M	13	Triamcinolone	8.4	12.8	50.4	37.6
8	41/M	1.5	Dexamethasone	3.6	6.0	13.4	13.1
9	43/F	6	Triamcinolone	21.6	7.4	11.8	8.6
10	55/F	14	Prednisolone	5.4	4.2	26.4	37.6
11	49/F	23	Prednisolone	36.0	6.8	33.2	—
12	48/F	4	Prednisolone	5.4	9.1	45.0	33.2
13	45/F	4	Triamcinolone	10.8	8.9	37.2	43.8
14	37/M	7	Triamcinolone	1.8	14.2	40.4	49.6
15	45/F	15	Prednisone	21.6	5.9	39.0	31.4
16	51/F	10	Prednisone	7.2	9.4	44.0	47.4
17	69/F	6	Triamcinolone	3.6	5.3	40.6	28.4
18	61/F	43	Betamethasone	18.2	3.0	22.4	10.8
19	53/F	10	Prednisolone	7.2	11.6	40.4	46.0
20	63/F	16	Triamcinolone	3.6	7.8	44.8	50.6
Mean	50.5	12.9		10.5	7.8	28.8	28.4
S.D.		11.6		8.9	3.1	14.0	15.9

or ACTH-responses to values exceeding four times the basal level of urinary 17-OHCS were observed in a few patients (subjects No. 13, 16, 19, 20). No significant differences could be observed in the suppression of endogenous hormone

TABLE 2

Details of Patients and Results of Urinary 17-OHCS Determinations During Basal Conditions and Following the Administration of Metyrapone or ACTH in Asthmatics who have not Received Adrenal Steroids.

Subject	Age/Sex	Duration of disease	Degree of severity	Urinary 17-OHCS mg/24 hours		
				Basal excretion	Response to metyrapone (750 mg q. 4 hrs. for 24 hrs.)	Response to i.v. ACTH
1	48/M	2 months	1°	14.9	24.2	25.2
2	38/F	3 "	1°	11.4	15.2	35.8
3	49/M	3 "	3°	14.4	25.4	49.5
4	26/M	6 "	2°	14.3	36.2	55.7
5	46/M	9 "	3°	14.6	20.0	23.4
6	36/M	1 year	3°	15.7	33.4	16.6
7	29/M	1 "	3°	13.8	21.8	34.0
8	34/F	1 "	1°	9.1	15.2	32.0
9	62/M	1½ years	1°	10.3	29.6	37.0
10	25/M	1½ "	2°	8.7	28.0	33.0
11	24/M	2 "	3°	13.0	34.0	28.4
12	53/M	3 "	1°	5.3	17.5	20.8
13	20/M	3 "	1°	11.2	25.0	56.0
14	52/F	3 "	1°	7.5	24.6	33.4
15	39/M	4 "	1°	13.3	30.4	34.4
16	41/F	4 "	3°	8.0	13.4	18.0
17	40/M	6 "	1°	21.0	42.3	47.7
18	57/M	10 "	3°	9.3	29.6	16.0
19	35/M	10 "	1°	17.2	25.0	39.6
20	49/M	10 "	3°	12.6	18.0	31.4
21	56/F	10 "	1°	10.4	29.7	59.0
22	55/M	12 "	3°	14.6	27.2	34.2
23	58/F	12 "	1°	12.2	17.6	28.6
24	54/F	12 "	1°	5.2	35.6	25.8
25	57/F	16 "	1°	9.2	36.8	39.3
26	19/F	17 "	2°	11.7	25.4	38.6
27	49/F	30 "	1°	9.9	25.2	32.4
28	68/F	40 "	1°	11.2	16.2	38.2
Mean	43.5	7.6		11.8	25.8	34.4
S.D.		9.0		3.6	10.5	13.5

production produced by the various types of adrenal steroids administered during the course of the study.

Table 2 shows the basal excretion values of urinary 17-OHCS and the results of metyrapone and ACTH-tests performed in asthmatic patients who have not received adrenal steroids arranged in order of the duration of the disease. Patients included in this group had chronic asthma of the endogenous type except for four patients (subjects No. 4, 9, 11 and 12) who had exogenous asthma the severity of the asthmatic condition being variable as indicated in the table.

Metyrapone was in this group of asthmatics administered in a dose of 750 mg given four-hourly for 24 hours and the urinary excretion of 17-OHCS was measured during the administration of the blocking agent and during the following day when the most pronounced response was seen in part of the patients. The highest 17-OHCS excretion value measured on either of these days has been used for the evaluation of the metyrapone response. An increase of the urinary 17-OHCS excretion to less than twice the basal excretion level which in most cases was accompanied by a normal or slightly elevated basal excretion and an adequate response to ACTH was observed in eight asthmatic patients (subjects No. 1, 2, 5, 8, 16, 19, 23 and 28) while an increased basal excretion of urinary 17-OHCS and/or a hyperreactive ACTH-response was seen in three patients (subjects No. 4, 17, and 21). In all the other patients the basal excretion of urinary 17-OHCS as well as the results of the metyrapone and ACTH-test were found to be within normal limits.

No significant correlation could be observed between the basal urinary 17-OHCS levels and the metyrapone or ACTH responses on the one hand and the duration of the disease or the clinical severity of the asthmatic condition on the other.

DISCUSSION

The subnormal metyrapone and/or ACTH responses observed during the course of the present study in part of the

asthmatic patients who had received long-term treatment with adrenal steroids suggest suppression of the endogenous hormone production caused by the prolonged administration of corticosteroids.

These findings are in agreement with the results of our previously published investigation (*Jakobson et al.* 1968) in which defective metyrapone and/or ACTH responses were observed in a comparatively larger number of steroid-treated asthmatics than in the present study. The difference between the two groups of asthmatic patients can probably in part be explained by the somewhat longer duration of treatment and the somewhat larger administered total dose of adrenal steroids in the former group of patients. Metyrapone was on the other hand in the previously studied group of patients administered for 24 hours while a 48-hour metyrapone test was carried out in the steroid-treated asthmatic patients during the course of the present study. Prolongation of the metyrapone test to 48 hours has been advocated by some authors (*Brownie & Sprunt* 1962, *Pekkarinen et al.* 1963) who have felt that the administration of metyrapone for 24 hours which was originally suggested by Liddle and co-workers in 1959 is not always sufficient for the evaluation of the pituitary ACTH-secretory capacity. Our studies do not afford any definitive conclusions regarding the optimal dosage of metyrapone because the two above mentioned groups of asthmatic patients were not entirely comparable and the metyrapone response was moreover in the previously studied group of asthmatics evaluated by means of the increase of urinary 11-deoxy-17-hydroxycorticoids and in the present study by means of the increase of urinary total 17-hydroxycorticoids produced by the administration of the blocking agent.

The metyrapone response was during the course of the present study similarly as in our earlier report found to be more easily suppressed in steroid-treated asthmatics than the ACTH-response and these findings would seem to offer additional support for the previously expressed view that the suppressive effect of the long-term adrenal steroid therapy is

mainly exerted at the pituitary level or at higher cerebral centers concerned with the control of ACTH secretion by the anterior pituitary.

The somewhat subnormal metyrapone responses observed following the administration of metyrapone for 24 hours in a few asthmatic patients who had not received adrenal steroids can perhaps also be accounted for by an incomplete blocking of the 11-beta-hydroxylation in the adrenal cortex by an insufficient dose of metyrapone although diminished pituitary responsiveness to the administration of the blocking agent can on the other hand not be completely dismissed as an alternative explanation. In the other asthmatic patients who had not received treatment with adrenal steroids pituitary-adrenal function was during the course of the present study found to be within normal limits.

The evidence presented by previous authors in favour of a pre-existing depression of adrenocortical function in asthmatic patients consists mainly of the investigations of earlier workers who have found a low excretion of urinary 17-ketosteroids in asthmatics during basal conditions or following the administration of ACTH (*Rackemann 1945, Eriksson-Lihr 1951, Andersson 1953*). A relative adrenocortical insufficiency has also been claimed on the basis of epinephrine and insulin tests (*Eriksson-Lihr et al. 1949*). The excretion of urinary 17-ketosteroids reflects, however, in addition to glucocorticoid secretion androgenic steroid formation and is known to vary with age. Chronic illnesses and malnutrition diminish also the excretion of urinary 17-ketosteroids which cannot be regarded as very reliable in diagnosing mild forms of adrenocortical hypofunction. More recently a normal excretion of urinary 17-ketosteroids in patients with asthma has been reported by other workers (*Davies 1956, Reinberg et al. 1963 and Blumenthal et al. 1966*).

The excretion of urinary glucocorticoids or urinary 11-hydroxysteroids has also been reported to be low during an asthmatic attack (*Spaner et al. 1960*) while several other workers (*Davies 1956, Kass & Appleby 1960, Reinberg et al. 1963*

and *Blumenthal et al.* 1966) in agreement with our studies have found normal basal levels of urinary 17-hydroxycorticoids in asthmatic patients and an adequate response to ACTH.

A poor plasma cortisol response to ACTH in asthmatic patients was reported by *Johnson & Skanse* (1952) and more recently by *Robson & Kilborn* (1965) while normal plasma 17-OHCS responses to ACTH have been observed by other workers (*Quarles van Ufford* 1953, *Serafini and di Nardo* 1955). *Siegel et al.* (1956) on the other hand found significantly higher plasma levels of 17-OHCS in patients with severe symptoms than in asymptomatic or mild asthmatics and a significant increase of plasma cortisol levels during asthma over corresponding baseline values was also observed by *Blumenthal et al.* (1966). These findings as well as the increased excretion of urinary 17-OHCS which during the course of the present study was observed in a few asthmatic patients can probably be ascribed to the stress-effect of severe asthma.

Other indices of pituitary-adrenal function which have been evaluated in asthmatic patients include estimations of the cortisol production rate which was found to be within the normal range when the patients were resting and their asthma was quiescent (*Robson & Kilborn* 1965). *Arnoldsson & Helander* (1963) found increased levels of steroid excreted in the urine in response to pyrogens while *Sundberg et al.* (1968) recently studied the effect of the Finnish sauna-bath on the urinary excretion of 17-hydroxycorticoids and found no effect in asthmatic patients in contrast to healthy subjects. This was thought to be due to the fact that the sauna-bath represents a minor form of stress which is not comparable to the administration of pyrogens.

Few studies have so far been concerned with the metabolism of adrenocortical hormones in asthmatic patients which might offer an explanation for the suggested inadequate adrenal function or the inadequate adrenal response to stress which has been reported by some authors. *Dwyer et al.* (1967), however, recently measured the metabolic clearance

rate of cortisol (MCR) after a constant infusion of tracer doses of radioactive cortisol and found a normal response to hydrocortisone injection in non-steroid treated asthmatic patients and a normal rate of cortisol metabolism. In long-term steroid-treated patients on the other hand an increased rate of cortisol metabolism was demonstrated which was thought to indicate the need to administer relatively large initial doses of cortisol to steroid-treated asthmatics which also according to clinical experience are often required in these patients during status asthmaticus to achieve a satisfactory therapeutic response.

Several factors must be taken into consideration in explaining the often conflicting reports on pituitary-adrenal function in asthmatic patients. In addition to the shortcomings of such methods as 17-ketosteroid determinations or bioassay procedures with a poor reproducibility which have been in use in some of the earlier studies incomplete urine collections or improper timing of the samples can even under the best of conditions adversely influence the results of all studies based on the estimation of the corticosteroid content of urinary specimens. Concomitant diseases, especially endocrine disturbances, liver diseases and renal affections, the nutritional status of the patients and the administration of adrenaline or other medications might also influence corticosteroid levels and most reports do not mention whether efforts have been made to exclude such factors in the selection of the subjects for the study.

It can be concluded that regardless of the differing results obtained by various workers most of the studies performed during recent years do not offer any convincing evidence that patients who have not received adrenal steroids in general would exhibit any serious defects of pituitary-adrenal function or display signs of a deranged metabolism of adrenocortical hormones. It can on the other hand not be excluded that individual asthmatics, in particular those with long-standing severe asthma with associated complications or concomitant diseases, may have subnormal corticosteroid

levels which possibly may aggravate the asthmatic state. There is furthermore some evidence of reduced adrenal responsiveness to certain forms of stress in asthmatic patients. This is, however, not necessarily indicative of a primary defect of adrenocortical function in bronchial asthma and can probably in most cases be attributed to chronic disease and associated factors. The administration of adrenal steroids to asthmatic patients on the basis of a pre-existing depression of adrenocortical function would thus seem to be justifiable only under exceptional circumstances and the well-known suppressive effect of prolonged adrenal steroid therapy on the endogenous hormone production must always be kept in mind whenever corticosteroid treatment is deemed advisable in intractable cases of bronchial asthma.

SUMMARY

Pituitary-adrenal function was compared in 20 steroid-treated asthmatic patients in whom the mean duration of continuous adrenal steroid therapy was 3.1 years and in 28 asthmatic patients who had not received adrenal steroids. The mean excretion of urinary 17-OHCS in the steroid-treated group of patients was 7.8 mg/24 hrs during basal conditions and 28.8 mg/24 hrs during the intravenous administration of ACTH and the corresponding mean values in the asthmatics who had not received adrenal steroids were 11.8 mg/24 hrs and 34.4 mg/24 hrs respectively. The difference in the basal excretion of urinary 17-OHCS in the two groups of patients was found to be statistically significant. A subnormal response of urinary 17-OHCS to the administration of metyrapone was in the steroid-treated asthmatic patients in whom the metyrapone blocking agent was administered in a dose of 750 mg given four-hourly for 48 hours observed in six out of 20 patients and in four of these six patients the ACTH response was also defective. Two additional steroid-treated asthmatics showed a subnormal basal excretion of urinary 17-OHCS.

A normal basal 17-OHCS excretion and an adequate

ACTH-response was observed in all asthmatic patients who had not received adrenal steroid therapy. Following the administration of metyrapone for one day an increase of the urinary excretion of 17-OHCS consisting of less than twice the basal value was observed in eight out of 28 patients and the slightly impaired metyrapone response was in these cases attributed to an insufficient dosage of the blocking agent. Three asthmatics who had been treated without adrenal steroids showed signs of adrenocortical hyperactivity.

A short review of previous investigations concerning pituitary-adrenal function in asthmatic patients is presented. It is concluded that although a depression of pituitary-adrenal function can often readily be demonstrated in steroid-treated patients especially after prolonged administration of large doses of corticoids the results of the present study do not, in conformity with most other recently published works, offer much evidence of a pre-existing depression of pituitary-adrenal function in asthmatic patients who have not received treatment with adrenal steroids.

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