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ADRENAL CORTICAL FUNCTION IN BRONCHIAL ASTHMA AND ITS DIAGNOSTIC VALUE

By

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In 1949, in the beginning of the ACTH era, *Eriksson-Lihr et al.* (1, 2) reported a reduced adrenal function in allergic conditions. They found *Kepler's* test positive in 32 out of 169 cases of bronchial asthma although the test must be considered non-specific. In 24 out of 96 cases of allergic conditions (no specific diagnosis were recorded) the 17-ketosteroid excretion was found to be inferior to the normal values found by *Hamburger* (3); in 6 cases it was found considerably above the normal values. The reducing corticoids in the urine were also examined in 36 patients suffering from bronchial asthma, and what was called "sub-normal" values were found in 27 cases.

Two years later *Venning et al.* (4) examined the excretion of 17-ketosteroid and reducing corticoids in 12 asthma patients; they found the mean steroid excretion to be lower in asthma patients than in healthy subjects. *Rose* (5) found low 17-ketosteroid and reducing corticoid excretion in the urine in 53 cases of bronchial asthma, although the excretion was higher in patients with hereditary dispositions to allergic diseases, with positive skin reactions, or exogenous causes for their diseases as compared to subjects with no such dispositions, reactions, and causes. The former group was also found to respond better to the ACTH treatment, showing periods of remission of up to six months, as compared to the latter

TABLE I

The excretion of 17-ketosteroid and reducing corticoids in the urine in 25 severe bronchial asthma patients.

Pt. No.	Sex	Age in years	Height i cm.	Weight in kg.	Duration in years	Eosino- phils in blood per cmm.	17-ketosteroid		Reducing corticoids	
							Value de- termined mg/24 hours	Average normal value mg/24 hours	Value de- termined mg/24 hours	Average normal value mg/24 hours
3-52	♂	24	170	65.3	5	469	11.4	14.0	0.67	0.88
211-52	♀	18	159	51	10	580	1.9	7.5	0.14	0.62
251-52	♂	34	181	69.1	32	312	3.7	12.7	0.72	0.87
1545-52	♀	38	151	51.8	16	450	4.3	6.0	0.35	0.67
1736-52	♂	28	180	75.7	11	313	6.4	13.6	0.39	0.88
2476-52	♂	46	169	63	18	1000	6.2	10.3	0.46	0.80
2524-52	♂	17	173	51	12	512	9.9	9.9	0.41	0.76
2692-52	♂	58	169	77	1	830	4.5	7.8	0.58	0.70
3072-52	♀	45	157	55.9	1	500	1.4	5.7	0.40	0.63
3085-52	♂	41	180	74.6	1 1/2	690	7.4	11.1	0.72	0.82
3302-52	♀	23	155	53.3	18	412	7.3	8.6	0.42	0.69
3540-52	♀	56	148	57.1	19	780	3.0	4.9	0.48	0.59
3704-52	♀	22	142	52.7	4	638	3.3	8.7	0.33	0.69
3885-46	♂	44	173	68.5	16	531	3.1	10.8	0.61	0.81
1496-47	♂	31	175	71.6	29	830	7.2	13.1	0.44	0.89
2185-47	♂	19	156	68	13	834	5.7	11.3	0.59	0.80
1455-48	♀	50	159	63.2	8	731	3.2	5.3	0.86	0.61
2113-49	♂	36	165	70.5	4	320	11.4	12.0	0.81	0.87
3620-49	♀	26	171	61.1	18	326	6.1	8.9	0.36	0.70
4147-50	♀	25	166	62.3	11	564	6.3	9.0	0.58	0.70
1945-51	♂	70	178	68.8	4	750	4.9	5.5	0.51	0.60
3970-51	♂	56	171	87	22	708	7.0	8.5	0.60	0.72
4746-51	♂	65	160	73	1 1/2	550	5.3	6.1	0.54	0.65
2705-47	♂	31	169	65	3	620	7.1	13.1	0.50	0.88
1447-46	♀	66	151	52.9	22	470	3.3	3.9	0.43	0.52

Averages in the 25 asthma patients: 5.65 9.13 0.52 0.73

group where the period of remission did not exceed four weeks.

The present investigation was undertaken to determine the excretion of 17-ketosteroid and reducing corticoids in the urine in patients suffering from bronchial asthma; to compare the values thus found with *Hamburger's* and *Sprechler's*

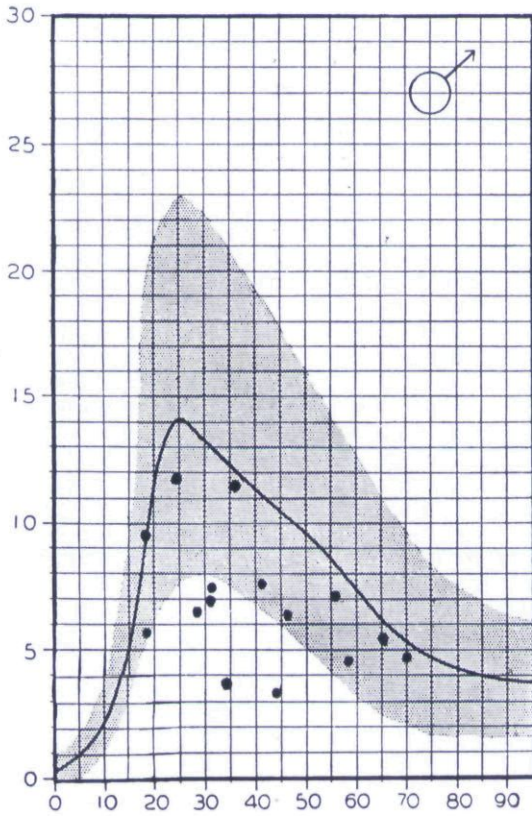


Diagram I.

17-ketosteroid excretion in 15 male patients suffering from severe bronchial asthma.

(3, 6) normal material; and to compare the adrenal cortical function in asthma patients and healthy subjects by measuring fluctuations in the eosinophils after non-specific influences on the sympathetic nervous system.

Table I and diagrams I, II, III, and IV, record the excretion of 17-ketosteroid and reducing corticoids in the urine to be lower in allergic patients than in healthy subjects. The mean values from the 25 asthma patients were 5.65 mg/24 hours as against the corresponding values in healthy subjects which averaged 9.13 mg/24 hours. A determination of the

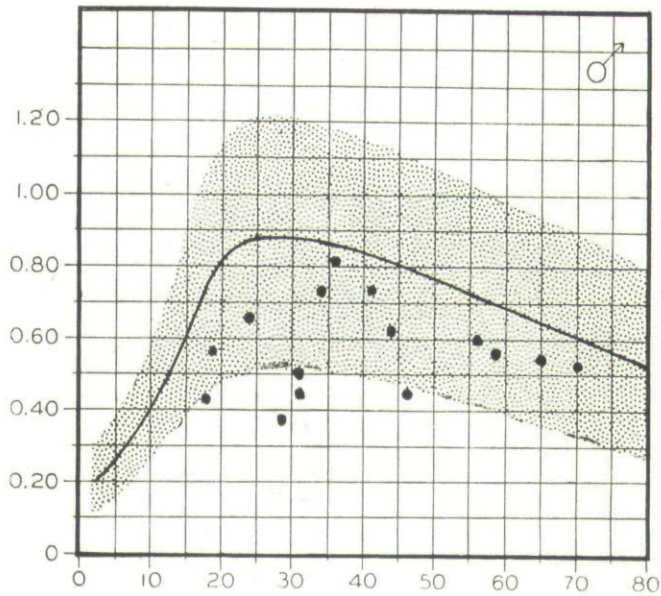


Diagram II.

Excretion of reducing corticoids in 15 male patients suffering from severe bronchial asthma.

reducing corticoids in the urine revealed only one case in which the amount exceeded the normal value; in all other cases the excretion was lower, averaging 0.52 mg/24 hours in the 25 asthma patients as compared to the normal average of 0.73 mg/24 hours. There was no obvious correlation between the duration of the asthma and the deviation from normal mean values. Eosinophilia was observed in all patients examined, but no correlation was found between the eosinophilia and low steroid excretion. The body height and weight of all subjects were registered without indicating any relation between deviations from normal body weights and low steroid values. All examinations were performed on out-patients who were carefully instructed to collect all urine during the 24 hours of examination. Many controls ensured examinations on our out-patients to be equally exact as examinations performed on hospitalized patients.

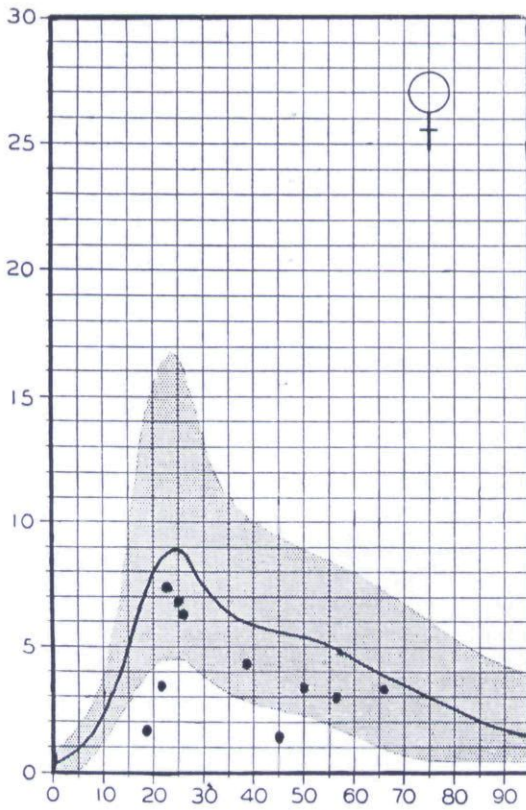


Diagram III.

17-ketosteroid excretion in 10 female patients suffering from severe bronchial asthma.

Selye (7) explained the findings of low steroid excretion in the urine as the result of a protracted stress to which asthma patients are subjected which result in an impaired adrenal cortical function.

The low 17-ketosteroid and corticoid excretion in the urine of asthma patients might, however, also be presumed due to the fact that stress in such patients fail to increase the production of ACTH. The distinction thus found might therefore be no expression of a reduced adrenal cortical function, but rather an indication of the different responses

TABLE II

Number of eosinophils per cmm blood before and after administration of 0.5 mg histamine to 10 normale.

No.	Sex	Age	Eosinophils per cmm before administration	Eosinophils per cmm $\frac{1}{2}$ hours after administration	Change in %
1	♂	20	186	114	÷ 38
2	♂	24	248	162	÷ 35
3	♀	21	46	0	÷ 100
4	♂	27	124	16	÷ 89
5	♀	51	425	150	÷ 64
6	♀	23	88	75	÷ 15
7	♀	19	125	148	+ 16
8	♂	38	494	463	÷ 6
9	♂	27	68	20	÷ 70
10	♂	31	102	78	÷ 24

towards stress of asthmatic patients and normal subjects. In the opinion of Long (8) ACTH is released in two different ways: (1) by a self-regulating humoral system, and (2) as a response to an influence on the sympathetic nervous system.

TABLE III

Number of eosinophils per ccm blood before and after administration of 0.5 mg histamine in 10 bronchial asthma patients.

No.	Sex	Age	Eosinophils per cmm before administration	Eosinophils per cmm $\frac{1}{2}$ hours after administration	Change in %
1	♀	32	3100	3420	+ 10
2	♀	27	520	610	+ 15
3	♂	38	962	1452	+ 34
4	♀	57	410	415	+ 1
5	♀	38	715	1050	+ 33
6	♀	35	506	563	+ 11
7	♂	49	150	338	+ 122
8	♂	31	988	1550	+ 57
9	♂	52	488	1000	+ 112
10	♀	56	412	788	+ 88

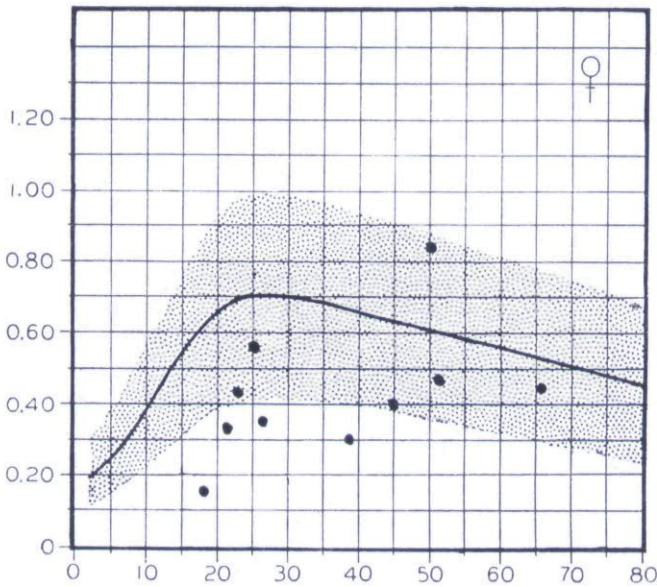


Diagram IV.

Excretion of reducing corticoids in 10 female patients suffering from severe bronchial asthma.

Thus it is reasonable to assume that *Addison's* disease and *Cushing's* syndrome are due to a dysfunction in the former system whereas allergic patients suffer some dysfunction in the latter. The possibility of a primary reduction in the adrenal cortical function is improbable since the inference must then be that allergic conditions would be frequent complications to *Addison's* disease which is well known to be incorrect.

In order to further elucidate this assumption asthma patients and healthy subjects were examined as to their responses to influences on the sympathetic nervous system. Histamine was used as provoking agent because it was considered sufficiently non-specific to represent an arbitrary stress. Adrenaline and Ephedrine could not be used because they as well as kindred compounds probably are active in the first stage of the stress mechanism (9). *Gray et al.* (10) found Histamine to be one of the compounds which easily releases the

ACTH from the pituitary; ACTH was found released a few seconds after intravenous Histamine injections.

The experimental technique was as follows: 0.5 mg Histamine was administered subcutaneously to 10 healthy subjects; the eosinophils were counted (11, 12) immediately before and 30 minutes after administration. The findings are recorded in table II indicating a decrease in the circulating eosinophils in all cases but one. The case which did not conform to pattern, and in which an increase in the circulating eosinophils was observed, was thoroughly examined with a view to allergic conditions and pheochromocytoma; nothing was found apart from a certain sensitivity towards Histamine; the patient felt poor immediately after the injection, she became flushed in the face, and suffered a slight dyspnoea and headache; the blood-pressure remained normal, and apart from a slight headache the patient recuperated within 15 minutes. The decrease of the eosinophils was followed for one subject in order to elucidate in detail how soon after the injection the decrease set in, and how long it remained at a low level. The eosinophils were counted immediately before the administration of the Histamine and at ten-minute-intervals for one hour after the injection. The results are recorded in diagram V showing a fall in the eosinophils to set in very soon after the injection, later a raise to the normal level.

Similar experiments were performed on ten patients suffering from bronchial asthma who were injected subcutaneously with 0.5 mg Histamine. The eosinophils were counted immediately before and 30 minutes after the injection. A diagram of one case was drawn in which the eosinophils were counted immediately before the administration and at ten-minute-intervals for one hour after the injection. The findings are recorded in table III and diagram V and show first a heavy increase in the circulating eosinophils within the first ten minutes; then a slow decrease until one hour later when the original level is reached. After the injection most of the patients felt poor with dyspnoea and ronchi; five minutes after the injection one patient suffered a severe attack of

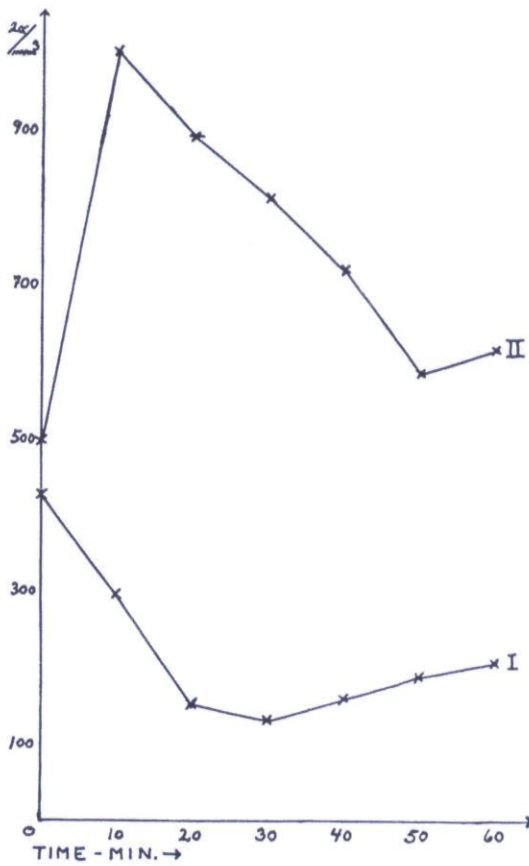


Diagram V.

Number of eosinophils per cmm blood after administration of 0.5 mg Histamine to one healthy subject I and to one patient suffering from bronchial asthma II.

The Histamine was administered at noon.

asthma which was relieved by an intravenous theophyllamine injection.

If these findings prove to be generally valid the eosinophil reactions towards external influences must be considered different in allergic and non-allergic subjects, and the above method might thus be applied as a diagnostic aid in determining whether a patient is allergic or non-allergic.

The above findings are consistent with *Dragsted's* (13) findings in allergic rhinitis, where allergic patients on direct exposition react with a raise in the circulating eosinophils, whereas the same patients after specific de-sensitization react with a fall in the eosinophils on repeated exposition. After de-sensitization a clinical improvement was found in these patients. Such patients may thus be assumed to respond normally instead of allergically after specific de-sensitization. The above explains also to some extent why de-sensitization with Histamine is successful in some instances, since any kind of specific or non-specific de-sensitization may influence the stress mechanism so as to make the patient react normally to external influences.

Another question which is still open to discussion is whether an ACTH treatment as now administered is capable of reversing an allergic organism to normal reaction for any longer period or whether the effect is merely a temporary, induced condition which resembles stress. It seems, however, justifiable to consider an allergic condition as a defect in the so-called stress-axis (the sympathetic nervous system, the hypothalamus, the pituitary, and the adrenal cortex). *Hume et al.* (14) report that the hypothalamus exerts a humoral influence on the pituitary so as to increase the ACTH production.

If this is correct, an allergic condition might be interpreted equally well as a dysfunction of the hypothalamus as of the pituitary, or of the adrenal cortex, and the allergic condition might be treated by a specific or a non-specific de-sensitization by which the patient be made to respond with normal reactions, or by a substitution therapy with ACTH or Cortisone.

SUMMARY

The investigation was undertaken to determine the adrenal cortical function in 25 patients suffering from bronchial asthma. The 17-ketosteroid and reducing corticoid excretion in the urine was measured and compared with the findings

from *Hamburger's* and *Sprechler's* normal material. The values are found to be lower in allergic than in normal subjects.

The fluctuation in the circulating eosinophils was examined, after administration of 0.5 mg Histamine, in ten normal subjects and in ten patients suffering from bronchial asthma. The eosinophils were found to decrease in normal and increase in allergic subjects.

The probability of applying this test as a diagnostic aid to determine whether or not a patient is allergic is discussed.

The pathogenesis of allergic conditions is finally discussed.

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