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PITUITARY FUNCTION IN PATIENTS WITH
BRONCHIAL ASTHMA MEASURED INDIRECTLY
BY METHOPYRAPONE (SU 4885)

By

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For a number of years the adrenocortical function in allergic patients has been the subject of intensive research. In 1949 *Eriksson-Lihr et al.* (1) found adrenocortical function to be reduced in asthmatics, and their results were later confirmed by *Wenning et al.* (2).

Johnson & Skanse (3) believe that allergic subjects have a poor balance between the various adrenocortical functions. *Andersson* (4) found 17-ketosteroids and reduced corticoids to be lower in asthmatics than in normal persons. Thus, since the function of the adrenal cortex appears to be reduced in allergic patients, it seemed of interest to study their pituitary function. The present investigation was carried out to study the pituitary function in allergic patients.

This can now be done by measuring the ACTH production indirectly by methopyrapone (*Liddle* (5)). This method is based on the theory that a reduced secretion of cortisol by the adrenal cortex induces a compensatory increase in the pituitary production of ACTH. In small doses methopyrapone can inhibit 11-beta-hydroxylase in the adrenal cortex. As a result of this inhibition the adrenal cortex forms, instead of cortisol, 11-desoxycortisol, also called compound S. Unlike cortisol, this substance has little inhibitory effect upon the pituitary ACTH production. When the blood level of cortisol falls, there will be a marked increase in the formation of compound S

in the adrenal cortex. This increase may be measured by determining the urinary 17-ketogenic steroids, as compound S is a 17-hydrocorticoid.

METHODS

Methopyrapone was administered in doses of 500 mg every 4 hours for 24 hours, a total of 3 g. The excretion of 17-ketogenic steroids in the 24-hour urine was determined 24 hours before, during, and 3 days after the administration of methopyrapone. An ACTH test was performed by the administration of 25 units ACTH twice in 24 hours. The 17-KGS were determined 24 hours before, during, and 24 hours after the administration of ACTH.

RESULTS

First, the effect of methopyrapone was investigated in 10 normal persons *i.e.* persons with no history or objective signs of endocrine or allergic disorder. The results are given in Table 1 which shows that during the first or second day after the administration of methopyrapone there was a marked increase in the urinary excretion of 17-KGS. This must be interpreted as a sign of increased pituitary production of ACTH. The increase averaged 110 per cent, the maximum being 180 per cent and the minimum 78 per cent.

Thereupon, the effect of methopyrapone upon 8 patients with severe bronchial asthma was investigated. The patients had been suffering from asthma for periods ranging from 4-10 years. None of them had been treated by steroid, and they had no history or objective signs of endocrine disorder.

The results of the methopyrapone test are shown in Table 2. It will be seen that in all cases there was an increase in 17-KGS within the 1st or 2nd day after administration of methopyrapone, but this increase was considerably less marked than that seen in the normal subjects. The average increase was only 43 per cent, minimum 30 per cent, and maximum 70 per cent. Six of the 8 asthmatics, who showed only a slight increase during the methopyrapone test, were submitted to an ACTH test. In all 6, this test was positive, *i.e.* an increase in urinary 17-KGS exceeding 50 per cent after the administration of ACTH.

TABLE 1
*Pituitary Function in 10 Normal Persons Determined
 by the Methopyrapone Test.*
 17-KGS mg/24 hours.

Case No.	Before methopyrapone		After methopyrapone			Increase in %
	- 1 day	0 day	+ 1 day	+ 2 days	+ 3 days	
1	6.2	7.1	10.2	17.8	10.1	180
2	5.4	6.2	9.1	16.9	9.3	124
3	6.8	6.4	16.2	12.5	8.9	116
4	7.3	7.8	17.1	17.3	9.2	139
5	8.2	8.9	12.2	16.8	8.1	64
6	7.4	10.8	9.8	22.8	9.1	134
7	8.4	7.9	15.9	13.4	7.3	78
8	6.8	6.4	17.8	19.2	10.3	80
9	7.6	8.2	17.4	12.3	9.4	87
10	6.3	7.2	12.6	14.1	8.3	98
Average increase						110

TABLE 2
*Pituitary Function in 8 Patients with severe Bronchial Asthma Determined
 by the Methopyrapone Test.*
 17-KGS mg/24 hours.

Case No.	Before methopyrapone		After methopyrapone			Increase in %
	- 1 day	0 day	+ 1 day	+ 2 days	+ 3 days	
1	9.5	8.7	15.1	9.0	7.8	31
2	10.0	11.1	15.4	14.7	12.0	42
3	7.6	7.7	11.4	11.0	9.4	47
4	5.4	7.4	9.4	11.9	4.4	65
5	7.6	8.2	10.4	10.3	6.3	30
6	8.7	10.5	17.1	15.7	7.0	70
7	8.1	10.7	15.0	11.8	9.7	42
8	8.5	7.7	14.2	9.0	6.3	43
Average increase						46

DISCUSSION

As is apparent from Tables 1 and 2 normal subjects as well as asthmatics showed an increase in 17-ketogenic steroids after administration of methopyrapone. This increase was considerably less marked in the asthmatics than in the normal persons. A reduced pituitary function is known to manifest itself by a reduced or abolished increase in urinary 17-ketogenic steroids after administration of methopyrapone (*Liddle*).

It is known also that patients having a destroyed pituitary gland or a chromophobe adenoma show no increase upon administration of methopyrapone. It, therefore, seems as if the reduced response to the methopyrapone test in asthmatics is interpretable as a reduced function of the ACTH producing pituitary cells, when disorder of the adrenal cortex can be ruled out.

Since all the patients included in the test had suffered from severe asthma for periods ranging from 4-10 years, it may be imagined that the reduced function is due to exhaustion of the hypophysis after the prolonged stress to which they had been exposed.

The reduction of the function was not as pronounced as that found in Addisonians whose steroid production is not sufficient to maintain the basal functions. In allergic patients the pituitary-adrenocortical function is reduced, so that they are unable to muster the excess production of steroids which is presumably needed by a patient in a state of alarm reaction.

Accordingly, there seems to be a simple explanation of the improvement obtained by steroid therapy in bronchial asthma: The patients are given the supplement of steroids needed during the constant stress to which they are exposed.

SUMMARY

The pituitary function in 8 asthmatics and 10 normal persons was investigated by the methopyrapone test.

The response to this test was found to be reduced in asthmatics as compared with normal subjects, the average increase in

17-ketogenic steroids being 45 per cent in the asthmatics against 110 per cent in the normal persons.

In a discussion of the findings it is deduced that asthmatics probably have a deficient reserve of pituitary-adrenocortical function owing to the constant stress to which they are exposed.

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