

ADRENO CORTICAL FUNCTION IN SEVERE ASTHMA

By

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It is known that before puberty more boys than girls have asthma. Between puberty and the menopause more women than men develop asthma. This suggests that a hormonal factor may play a part in the causation of asthma. Cortisone and corticotrophin rapidly relieve symptoms in most patients with asthma. Davies and Williams (1955) and Pickering (1952) suggested that an adrenal or pituitary defect might contribute towards the aetiology of asthma.

Brooks and Norymberski (1952) discovered that Sodium bismuthate oxidised a group of corticosteroids to 17 keto-steroids (17 KS). They named these corticoids (which include hydrocortisone, cortisone and their metabolites) 17 ketogenic steroids (17 KGS). Estimation of 17 KGS excretion is considered to be the most accurate index of adreno-cortical activity that can be provided by routine investigation (Hubble, 1955) and this excretion does not vary with age (Norymberski et al, 1953).

The excretion of 17 KGS has been measured on urine of patients who had been admitted to hospital with asthma, in an attempt to discover if there is evidence of adrenal hypofunction in asthma. In addition, in some cases steroid excre-

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tion was estimated while patients were receiving corticotrophin.

MATERIAL AND METHODS

36 patients were investigated, 26 women and 10 men. All had been admitted to hospital with asthma. 33 were admitted to hospital as 'emergency admissions' with acute asthma; 3 patients had had chronic intractable asthma for more than 3 months.

Some of the patients were considered to be more severely ill than others and, taking into account the history, the pulse and respiratory rates, the treatment necessary and the response to this treatment, the patients have been grouped into those with 'severe' and those with 'moderately severe' asthma. All patients who later received cortisone or corticotrophin were considered to be 'severe' cases.

Of the 26 women, 12 were considered 'severe' cases; 9 of these later received cortisone or corticotrophin.

Of the 10 men, 5 were considered 'severe' cases; 4 of these later received cortisone or corticotrophin.

All the patients were considered to have Intrinsic asthma, i.e. asthma in which infective and psychological factors are the important ones in producing symptoms. Routine treatment with adrenaline, intravenous aminophylline, antibiotics and the usual broncho-dilator drugs were not restricted, but none of these patients received cortisone or corticotrophin during the collection of the urine.

A 24 hour collection of urine was made within the first 48 hours of admission. Butt et al. (1950) have emphasised that this collection must be complete and that mistakes in collection are the major source of error in these estimations. The procedure was explained to the patient and no urine sample was accepted if the Ward Sister had any doubt as to its completeness. Creatinine excretion was measured in some cases. The steroids were then estimated, by the method described by Norymberski et al. (1953) with its modification (Gibson and Norymberski, 1954). 17 KS are first estimated, the urine is

TABLE A
Men.

	Age	17 KS (mg/24 hours)	17 KGS (mg/24 hours)
Severe Cases	72	4.5	8.7
	49	7.2	12.8
	65	7.0	12.7
	25	26.0	12.0
	64	8.5	6.3
<i>Average</i>		10.6	10.5
Moderately Severe Cases	50	3.5	9.4
	30	15.0	14.0
	42	4.4	5.6
	55	3.5	6.5
	36	5.3	8.0
<i>Average</i>		6.3	8.7
Normal Range		9-24	10-20
Total Average		8.5	9.6

then treated with sodium bismuthate and the total 17 KS estimated. Subtraction of the two results gives the level of 17 KGS.

As a result of 600 assays Hubble (1955) considers that the normal output of 17 KGS in men is 10-20 mg/24 hours and 5-15 mg/24 hours in women. We estimated the 17 KGS excretion of many 'normals' and all were within these ranges.

RESULTS

The average excretion of 17 KS + 17 KGS in the 26 women is within normal limit, while the average excretion of these steroids in the 10 men is just below the lower limit of normal. There is no difference between the 17 KGS excretion of the patients with severe and moderately severe asthma. The three

TABLE B
Women.

	Age	17 KS (mg/24 hours)	17 KGS (mg/24 hours)
Severe Cases	16	8.0	6.7
	26	4.9	5.1
	55	5.6	9.9
	64	4.6	20.4
	31	6.0	6.2
	55	6.2	5.8
	54	8.2	15.2
	36	7.1	7.1
	51	2.3	4.5
	72	3.0	6.4
	20	6.1	12.8
	45	5.0	4.6
<i>Average</i>		5.6	8.7
Moderately Severe Cases	73	9.2	10.0
	54	3.0	3.0
	23	5.5	9.3
	14	7.0	7.0
	28	9.0	9.0
	47	4.1	4.1
	51	10.7	12.1
	70	4.2	10.2
	27	10.4	10.8
	67	7.3	10.7
	56	5.0	4.0
	60	6.0	11.0
	53	13.0	13.5
	66	4.0	4.2
<i>Average</i>		7.0	8.5
Normal Range		5-17	5-15
Total Average		6.25	8.25

patients with intractable symptoms excreted normal amounts of 17 KS + 17 KGS.

Table C shows the examples of the effect of corticotrophin-

TABLE C

Examples of Steroid Excretion after Corticotrophin Gel.

Day	1	2	3	4	5	1	2	3	1	2	3	4
A.C.T.H. gel. (units)	0	80	80	80	80	0	80	80	0	80	80	40
17 KGS (mg) %	4.5	11.1	19	16	18.4	6.2	9.5	11.0	5.6	10	12.8	5.0
17 KGS (mg) %	8.7	36.0	43.0	57	58.6	5.8	18.5	45.5	9.9	21	51.2	26.2

gel on the excretion of 17 KS + 17 KGS in three patients. There is an immediate increase in the excretion of these steroids, showing that the adrenal cortex is able to respond to corticotrophin.

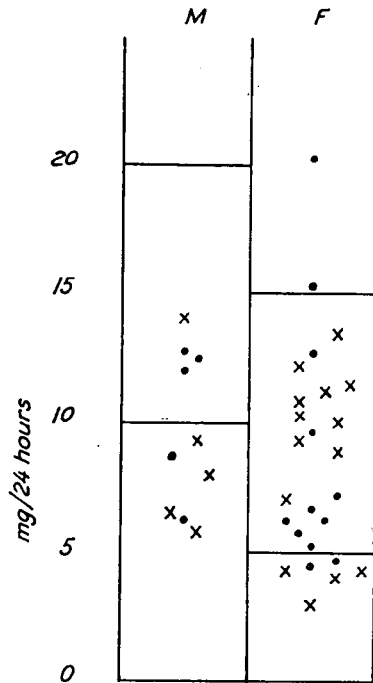
Generally symptoms subside rapidly once cortisone or corticotrophin is given but severe asthma can occur with a very active adrenal gland. A doctor aged 31, who had been receiving 80 units of corticotrophin gel for a week before admission had severe asthma yet he excreted 36.8 mg of 17 KGS on his first day in hospital. A housewife aged 39 was admitted with severe asthma despite treatment with corticotrophin gel. She excreted 57.8 mg of 17 KGS on her first day in hospital.

The effect of drugs given on the day the urine was collected must be considered. Most of the patients were given antibiotics, 15 received adrenaline and 10 were given intravenous aminophylline (5 severe and 5 moderately severe cases). Hunter et al. (1955) have shown that adrenaline does not increase adrenocortical secretion. The effect of I.V. aminophylline is not known but the 10 patients were not remarkable for a high output of 17 KGS.

DISCUSSION

17 Ketosteroid excretion reflects androgenic steroid formation in the body and is known to vary with age. In addition, chronic illness, and malnutrition diminish the excretion of 17

17 Ketogenic Steroids.



• Severe Cases

x Moderately Severe Cases

KS (Forbes et al., 1947). While the estimation of 17 KS is of great value in adrenal failure or cortical overaction (Butt et al., 1950) so many factors influence the excretion that the results do not help in diagnosing mild adrenal hypofunction. However, the 36 asthmatics did excrete on an average, amounts of 17 KS that were at the lower limit of the normal range.

Andersson (1953) studied the steroid excretion of 25 asthmatics and found a lower excretion of 17 KS + reducing steroids than in normal.

Rose and his associates have studied steroid excretion in allergic patients.

Venning et al. (1951) found that the average value of the urinary excretion of glucocorticoids, total corticoids and 17 KS was lower in patients suffering from rheumatoid arthritis and asthma than those observed in normal individuals.

Rose et al. (1955) extended the above observations. They studied the steroid excretion of 58 asthmatics. They found that the average excretion was lower than in normal subjects. They found that the average asthmatic male excreted considerably less steroid than did the normal male, but with the female asthmatic this difference was not so marked. They also found that severe asthmatics showed a lower average excretion than did moderate cases.

Our results do not confirm all the above findings. Some of our men seem to show evidence of adrenal hypofunction but we have found no correlation between severity of the asthma and 17 KGS excretion.

The difference in these findings may be due to the different methods used in measuring corticoid excretion. Rose and his colleagues measured glucocorticoids by biological assay and estimated formaldehydogenic steroids. It is believed that the estimation of 17 KGS is a more reliable measure of adrenocortical function. Norymberski et al. (1953) write that "bioassays are of limited value since corticoids are excreted in small quantities and very likely represent only a random fraction of the total urinary corticosteroids". When these results are considered with the rapid response of the adrenal to corticotrophin then I believe that there is no evidence of adrenal hypofunction in most of the women with severe asthma. 6 of the 10 men excreted amounts of 17 KGS below the lower limit of normal. No conclusions can be drawn from these few estimations but taken with the figures of Rose et al. (1955) they do suggest that there may be evidence of adrenal hypofunction in some men with severe asthma. Infection is generally the important factor in men admitted to hospital with severe asthma. In women psychological factors are generally more important. If further investigations confirm that there is a difference in the steroid excretion of men and women with

severe asthma then this possible explanation should be considered.

SUMMARY

(1) The urinary excretion of 17 Ketosteroids and 17 keto-genic steroids has been measured in 26 women and 10 men with severe asthma.

(2) Norymberski's method was used and this is considered to be a measure of adrenocortical function.

(3) The results show no evidence of adrenal hypofunction in most of the women but 6 of the 10 men excreted amounts of 17 KGS below the lower limit of normal.

(4) No relationship was found between severity of symptoms and 17 KGS excretion.

I am grateful to Dr. D. A. Williams for encouragement and for advice in the preparation of this paper. I wish to thank Mr. Robertson of the Asthma and Allergy Research Unit, Cardiff, who performed the numerous biochemical estimations.

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