Corticosteroid Therapy in Children with Asthma

Hypophyseo-adrenocortical Inhibition

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This investigation was designed to study the function of the hypophyseo-adrenocortical system in children with asthma, treated with long-term corticosteroids in small doses.

Methods and Subjects

The function of the hypophyseo-adrenocortical system was investigated by the method described by Robinson, Mattingly, and Cope (1962), based on the principle that if the system is functionally normal the blood cortisol level, which is decreased in the course of corticosteroid therapy, returns to normal after steroid withdrawal.

In a number of asthmatic children on steroid therapy the blood cortisol level was determined. Steroids were then stopped abruptly, and during the subsequent 7 days the blood cortisol level was determined on three occasions. On the 9th and 10th day, the reactivity of the adrenal cortex was determined following ACTH (Cortrophin-Z, Organon) 1.5 u./kg. intramuscularly on two successive days. This dose of ACTH is one that produces maximal stimulation. The blood cortisol level was determined on both days 4 hours after ACTH had been given, and the level was compared with that of the previous day.

The blood cortisol level was always determined at 8 a.m. ACTH, when given, was administered at 8 a.m., in which event the blood cortisol level at noon was determined. At the time of blood sampling, the test subject was in a basal condition (fasting, bed-rest for the previous 12 hours). For the determination of plasma cortisol, a fluorescence method was used, somewhat modified from that described earlier (Steward, Albert-Recht, and Osman, 1961; De Moor, Osinski, Deckx, and Steeno, 1962; Mattingly, 1962).

The following groups were examined:

1. 61 healthy children in whom the blood cortisol level was determined at 8 a.m.
2. 13 healthy children in whom the ACTH test was carried out.
3. 14 children with asthma, who had never been treated with steroids. In these patients the Robinson ACTH test was performed.

4. 29 children with severe asthma (see Table I), who had received prolonged daily doses of steroids. In these patients also the Robinson ACTH test was performed.

In all patients the investigation was carried out in the course of a clinically quiescent phase when there were no more than minimal symptoms or signs. None of the patients was suffering from discernible infection at the time of the test, all being under observation as hospital in-patients.

Results

Normal blood cortisol levels. The mean blood cortisol level at 8 a.m. in 61 physically healthy children was 15.5 $\mu\text{g./100 ml.}$ The standard deviation (SD) for this isolated test was 3.2 $\mu\text{g./100 ml.}$ From this it can be concluded that with the technique employed here, the blood cortisol level found in healthy subjects will, with a probability of 95%, range between 9 and 22 $\mu\text{g./100 ml.}$ (i.e. mean ± 2 SD). These values are in close agreement with those found by others (Bierich, Kersten, and Maruektad, 1959; van der Wal, Wiegman, Janssen, Delver, and de Wied, 1965; Hughes, Seely, Kelley, and Ely, 1962; Mattingly, 1963).

We have regarded as normal any value lying not more than 2 SD from the mean ($> 9 \mu\text{g./100 ml.}$). Values lower than the mean minus 3 SD have been regarded as *decreased* ($\leq 6 \mu\text{g./100 ml.}$). Values between 7 and 9 $\mu\text{g./100 ml.}$ have been regarded as *possibly decreased*.

In 28 duplicate determinations, the SD of the measuring error was 1.2. The 95% confidence interval of this SD amounts to 1.0-1.6. Measuring inaccuracy did not depend on the magnitude of the figure recorded, and the measuring error was small compared with the SD. Accordingly, no decimals have been given, and 0.5 has been rounded off to the nearest even figure.

The probability that a value of $\leq 6 \mu\text{g./100 ml.}$ will be found in a child that actually belongs to a population having a mean blood cortisol level of 16 $\mu\text{g./100 ml.}$ with a SD of 3 $\mu\text{g./100 ml.}$ is of the

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FIG. 1.—Mean blood cortisol level in healthy subjects and children with asthma; reaction to discontinuation of corticosteroid therapy and to ACTH. ● = 13 healthy subjects; × = 14 patients with asthma, not treated with steroids; ○ = 12 patients with asthma, treated with steroids, with normal blood cortisol level during treatment; Δ = 13 patients with asthma, treated with steroids, with decreased blood cortisol level during treatment.

order of 1 in 1000. This means that a finding of a decreased blood cortisol level almost certainly reflects the actual condition.

In a subject belonging to the population with a decreased blood cortisol level ($\leq 6 \mu\text{g./100 ml.}$), it is arguable that a blood cortisol level of $> 9 \mu\text{g./100 ml.}$ might be found under non-basal conditions (e.g. infection, trauma, or some other stress). In view of the observations on decreased blood cortisol levels (Table III) the probability of this occurring will be shown to be not more than 5%. The significance of a dubiously decreased value is less clear, because of the small number of observations. However, from the fact that so few values in the dubiously decreased range were obtained, we concluded that the classification used (normal versus decreased) was valid (see Table X).

Blood cortisol levels in patients and healthy subjects after ACTH. Clinical data and data concerning the treatment of patients are listed in Tables I and II. The results of the tests on asthmatic children are given in Tables III and IV, and of the healthy subjects in Table V. In discussing the group of patients treated with corticosteroids, we shall distinguish the categories *decreased blood cortisol during treatment* (Table III,

Nos. 1-13) and *normal blood cortisol during treatment* (Table III, Nos. 18-29).

In the category *decreased blood cortisol during treatment*, a pronounced increase usually occurred 48 and 72 hours after the discontinuation of steroids. This increase was significant ($p < 0.0001$; Friedman's test). Thereafter, no further rise was observed. In the category *normal blood cortisol during treatment*, no increase or decrease occurred (Fig. 1).

After each of the two doses of ACTH, all groups showed a significant increase of the blood cortisol level ($p = 0.001$). On the 5th day after the first dose of ACTH, the blood cortisol level had usually returned to the initial level observed before the test. There were no significant differences between the values on day 8 in the various groups (Fig. 1).

Application of the analysis of variance and the test of Scheffé* (all the tests being performed at the significance level of 5%) showed the following after the first dose of ACTH (Table VI, upper half):

(1) The increase recorded in the healthy subjects was significantly greater than in the patients not treated with corticosteroids.

(2) There was no significant difference between the increases recorded in the patients not treated

* The test of Kruskal and Wallis can also be used.

TABLE
Asthma Patients Treated

Case No., Sex, and Age at Onset of Asthma (yr.)			Symptoms Before and During Treatment						Constitutional Characteristics	Allergy (5) (skin reactions)			
			Attacks of Breathless- ness, Frequency and Duration (1)		Attack-free Periods; Frequency of Coughing, Breathlessness (2)		Attack-free Periods; Severity of Breathlessness (3)						
			During Last 12 Months							(4)	House Dust	Moulds	Pollen
			Before	During	Before	During	Before	During					
1	M	2	8	2	8	4	1	0	3	1	0	0	
2	M	1	8	4	8	8	2	1	0	3	1	0	
3	F	2	7-8	5	8	8	1	1	0	2	1	1	
4	F	1	6	2	5	1	1	0	2	3	3	0	
5	M	1	7	2	8	5	2	1	3	3	0	0	
6	M	2	8	5	8	8	1	1	2	2	0	0	
7	M	1	5	2	5	1	1	0	0	0	0	0	
8	M	2	7-8	2	4	1	1	1	3	1	0	0	
9†	F	4	7	12	8	8	1	1	0	0	0	0	
10	M	2	8	1	2	1	2	0	0	3	1	0	
11†	M	1	8	8	8	9	2	2	2	2	2	0	
12	M	1	8	2	2	1	0	0	3	4	0	6	
13	M	3	2	1	1	1	1	0	3	4	2	0	
14	M	4	8	1	8	8	1	1	2	3	3	1	
15	M	2	7-8	2	8	5	1	1	3	4	2	0	
16	M	5	5-8	1	4	4	1	0	2	0	0	0	
17	F	1	4	1	8	7	0	0	3	1	1	0	
18	M	1	6-8	1	2	1	1	0	3	3	0	0	
19	F	2	5-7	2	8	5	1	1	0	2	2	1	
20	M	3	2	1	4	1	0	0	2	3	1	0	
21	F	3	12	8	8	8	2	2	0	3	1	1	
22	M	1	5	1	5	1	0	0	2	2	0	0	
23	F	2	12	12	8	4	1	0	3	3	0	1	
24	F	2	4	1	5	1	0	0	3	1	0	0	
25	M	1	4	2	4	4	0	0	2	1	1	0	
26	F	2	8	8	4	1	1	0	3	3	1	0	
27	F	1	7	2	8	8	1	1	2	1	0	0	
28	M	1	9	2	8	8	2	1	2	1	0	0	
29	M	3	5	1	8	5	1	1	2	3	2	0	

† Patients 9 and 11 had reached puberty

(1) Attacks of breathlessness: frequency and duration (most frequent combination is listed)

Frequency	Duration	< 36 hr.	> 36 hr.	Highly Variable
≤ once per month ..		1	2	3
Once every 2 weeks ..		4	5	6
> once every 2 weeks ..		7	8	9
Highly variable ..		10	11	12

(5) Allergy (skin reactions):

Code	Largest Diameter Wheal (mm.)	Smallest Diameter Wheal (mm.)
0	0	0
1	4	1
2	7	4
3	10	7
4	> 10	10

(2) Attack-free periods: frequency of coughing and/or breathlessness

Breathlessness		Little or None	Moderate	Severe
Coughing, Wheezing				
None or at most 4 times a yr. for maximum of 14 days		1	2	3
6-8 times a yr. during 1-3 wk.		4	5	6
More often than once every 6 wk. with minimal duration of 1 wk.		7	8	9

(3) Attack-free periods: Severity of breathlessness

- 0 = none
 1 = little (occurring on cycling against wind, running)
 2 = moderate (occurring during climbing stairs, mild games)
 3 = severe (occurring during rest or mild effort)

(4) Constitutional characteristics:

- 0 = none
 1 = eczema, hay-fever
 2 = positive family history (eczema, hay-fever, asthma, chronic bronchitis)
 3 = 1 + 2

I

With Corticosteroids

Pulmonary Function (6) (during treatment)							Age at Examina- tion (yr. mth.)	No. of Years' Standing of Asthma	Duration of Treat- ment (mth.)	Total Drugs (mg.) (7)	Dosage Cortic. (mg./m. ² 24 hr.) During Last 6 mth.	
1 sec. Expira- tion	1 sec. Inspira- tion	Total Capacity	Residue	Reversi- bility Exp. and Insp.	Elasticity	Dead Space						Cortisone EQUIVA- lent (8)
2	1	0	0	1	0	0	9, 0	7	20	2400 p	5 p	20
1	0	0	0	1	0	0	14, 6	14	11	850 p	2.5 p	10
4	0	1	1	1	0	0	8, 11	7	32	3900 p	6-7 p	24-28
4	2	0	0	1	—	0	7, 11	7	29	1100 t	6 p	24
3	2	1	1	1	0	1	14, 6	14	18	> 4300 p	3.5 p	14
3	1	1	0	1	1	1	9, 10	8	12	3000 p	4 t	20
3	3	1	0	1	0	0	10, 6	10	27	< 100 p		
3	1	1	0	1	0	0	10, 2	9	17	300 t	5 p	20
4	3	0	1	1	0	0	11, 6	8	18	4000 p	5 p	20
5	1	1	3	3	1	—	11, 0	10	29	2600 p	2.5-5 p	10-20
4	3	—	—	9	—	—	13, 9	13	43	2400 p	0.4 b	13
4	2	1	3	9	—	—	11, 7	11	32	1500 p		
1	0	0	0	1	0	0	10, 4	8	30	250 b	0.6 b	20
3	2	1	0	3	0	0	13, 9	13	43	410 b		
3	0	1	0	1	0	0	11, 7	11	32	1500 p	0.5 b	16
3	0	1	0	1	0	0	10, 4	8	30	330 b		
3	0	1	0	1	0	0	12, 3	9	21	3800 p	4 p	16
3	0	2	1	2	0	0	8, 10	7	20	2900 p	2-4 p	8-16
3	0	1	0	1	0	0	9, 4	5	20	3500 p	6 p	24
3	0	1	0	1	0	0	8, 0	5	20	2700 p	5 p	20
4	1	0	0	3	0	0	12, 5	12	18	2900 p	3 p	12
1	1	—	—	1	—	—	11, 10	10	22	1800 p	2 p	8
3	2	1	0	3	0	0	10, 7	8	17	2000 p	2(4) p	8-(16)
2	0	—	—	1	—	—	8, 0	5	19	2700 p	4 p	16
2	1	—	—	1	—	—	10, 7	10	12	3600 p	8.5 p	34
3	1	1	0	3	1	0	6, 2	5	12	1100 p	2.5 p	10
3	1	1	0	3	1	0	12, 1	11	34	1000 p	3 p	12
1	0	1	1	1	0	0	10, 5	10	15	2500 p	1.25 p	5
2	0	1	0	1	0	0	11, 6	10	9	2200 p	5 p	20
3	1	1	0	1	0	0	9, 5	9	29	400 p	3-3.5 t	15-17.5
4	3	0	0	2	1	0	11, 10	11	21	355 t	3.75-5 p	15-20
							12, 7	10	8	2400 p	2.5-5 p	10-20
										650 p	2 p	8

(6) Pulmonary function:*

FEV₁ 0 = normal (> 75% of VC)

1 = 71-75%

2 = 61-70%

3 = 51-60%

4 = 41-50%

5 = 31-40%

6 = ≤ 30%

FIV₁ 0 = normal (> 90% VC)

1 = 81-90%

2 = 71-80%

3 = 61-70%

4 = 51-60%

5 = ≤ 50%

Total Capacity (TC)

0 = normal

1 = ratio TC patient/TC normal ≥ 115%

2 = ratio TC patient/TC normal ≤ 85%

Reversibility expiration and inspiration

Expiration Inspiration			
	Reversible	Not Reversible	Partially Reversible
Reversible ..	1	2	3
Not reversible ..	4	5	6
Partially reversible ..	7	8	9

Residue

0 = normal (20-25% TC)

1 = increased, completely reversible (aleudrin)

2 = increased, completely irreversible

3 = increased, partially reversible

* Normal values: H. Labadie, Laboratory for Pulmonary Physiology, Municipality Hospital, The Hague.

(6) Pulmonary Function (cont.)

Elasticity

0 = normal (3.5-5.5% of TC/cm.H₂O)1 = > 5.5% of TC/cm.H₂O2 = < 3.5% of TC/cm.H₂O

Dead space

0 = normal (≤ 30% of the VC)

1 = > 30% of the VC

(7) p = predniso(lo)ne

b = bethamethasone

t = triamcinolone

(8) 20 mg. cortisone = 5 mg. predniso(lo)ne = 0.6 mg. bethamethasone = 4 mg. triamcinolone.

TABLE
Data Concerning 14 Patients With

No.	Sex	Age at Onset of Asthma (yr.)	Age at Examination (yr., mth.)	No. of Years' Standing of Asthma	Symptoms During Last 12 Months Before Investigation			Constitutional Characteristics (4)
					Attacks of Breathlessness Frequency and Duration (1)	Attack-free Periods; Frequency of Coughing, Breathlessness (2)	Attack-free Periods; Severity of Breathlessness (3)	
1	M	1	8, 6	8	1	1	0	3
2*	F	1	13, 6	13	2	8	1	3
3	M	4	10, 10	7	8	8	1	0
4	M	1	10, 5	10	12 (variable)	7	1	3
5	M	3	10, 2	8	4	8	1	3
6	F	2	12, 8	11	1	9	2	2
7	M	4	10, 7	7	2	8	1	2
8	M	2	10, 8	9	7	8	1	1
9	M	2	11, 4	10	7	8	1	3
10	M	1	11, 8	11	12	8	2	3
11*	M	8	14, 10	7	4	5	1	3
12	M	2	10, 7	9	12	4	1	2
13	M	8	11, 1	4	6	7	1	2
14	M	2	8, 11	7	7	8	2	3

* Patients Nos. 2 and 11 were in early puberty, the others showed no external signs of puberty.
(1)-(6), see coding-key (Table I).

TABLE III
Blood Cortisol Level ($\mu\text{g./100 ml.}$) in 29 Asthma Patients Treated With Corticosteroids

Test Arrangement*														
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Determination No. ..	1	2	3	4	5	6	7	8	5 (ACTH)	6 (ACTH)	7			8
Patient No.	Determination No.													
	1	2	3	4	5	6	7	8						
1	2	7	9	12	24	33	40	6						
2	3	4	10	23	37	—	—	—						
3	5	13	14	15	22	38	38	11						
4	4	8	15	14	—	—	—	—						
5	5	12	16	13	20	32	28	8						
6	5	9	15	15	26	41	26	20						
7	1	1	11	8	18	22	29	7						
8	3	18	28	24	30	37	24	29						
9	3	13	12	8	20	29	29	10						
10	4	10	14	12	29	42	26	14						
11	1	1	2	5	10	17	24	6						
12	2	3	5	11	16	23	14	11						
13	6	11	11	12	17	26	11	14						
14	7	8	9	5	31	35	42	17						
15	9	12	14	12	32	38	28	10						
16	7	18	16	14	29	37	—	16						
17	9	17	21	17	31	31	39	14						
18	17	13	10	8	45	48	20	18						
19	14	11	14	13	36	44	—	13						
20	16	15	15	13	41	38	—	8						
21	10	11	11	11	18	31	38	12						
22	19	13	18	11	36	49	42	16						
23	10	10	—	—	30	37	37	10						
24	12	17	12	9	32	36	44	13						
25	14	28	21	15	43	—	56	18						
26	13	11	12	12	25	35	43	13						
27	18	23	18	17	28	33	24	12						
28	15	12	12	11	38	45	32	11						
29	13	15	15	13	44	48	59	20						

* Showing on which day each of the 8 cortisol determinations was made.

II

Asthma Not Treated With Corticosteroids

Allergy (5) (skin reactions)			Pulmonary Function (6)						
House Dust	Moulds	Pollen	1 sec. Expiration	1 sec. Inspiration	Total Capacity	Residue	Reversibility Exp. and Insp.	Elasticity	Dead Space
3	4	0	0	0	—	—	—	—	—
4	0	0	2	2	—	—	1	—	—
3	1	0	3	3	—	—	3	—	—
1	0	0	4	0	1	1	3	0	0
3	0	3	3	0	0	0	2	1	0
3	0	1	1	0	—	—	1	—	—
2	0	0	3	0	1	1	1	0	0
3	0	0	2	2	1	0	1	0	0
2	0	4	2	2	0	0	1	0	0
1	0	0	4	0	0	3	3	0	0
3	0	0	3	0	—	—	1	—	—
3	0	0	3	3	1	0	1	0	0
3	0	3	2	2	0	0	1	0	0
3	2	2	3	0	1	0	1	0	0

with steroids and those treated with steroids but exhibiting a normal blood cortisol level during the treatment. Furthermore, no tendency to significance can be observed.

(3) The increase in the patients not treated with steroids was significantly higher than in those treated with steroids but exhibiting a decreased blood cortisol level during the treatment.

(4) The increase recorded in the patients treated with steroids and exhibiting a normal blood cortisol

level during treatment was significantly greater than in those who exhibited a decreased blood cortisol level during treatment.

The following was found after the second dose of ACTH (Table VI, lower half).

(1) There was no significant difference between the increase in the healthy subjects and that recorded in the patients not treated with steroids.

(2) The increase in the patients not treated with steroids was significantly higher than in those treated

TABLE IV
Blood Cortisol Level ($\mu\text{g./100 ml.}$) in 14 Asthma Patients Not Treated With Corticosteroids

Test Arrangement*														
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Determination No. ..	1	2						3	4	5	6			7
								(ACTH)	(ACTH)					
Patient No.	1	2	3	4	5	6	7							
1	12	10	9	39	66	43	20							
2	9	12	10	43	48	26	16							
3	14	12	14	51	56	48	12							
4	13	14	10	47	64	46	15							
5	10	10	10	44	64	33	10							
6	28	17	18	29	49	48	25							
7	14	8	11	35	63	40	14							
8	14	14	15	28	51	38	13							
9	26	20	19	32	56	33	16							
10	14	14	12	37	51	45	11							
11	12	12	13	21	41	42	13							
12	17	12	15	22	49	35	12							
13	15	17	17	38	52	50	21							
14	24	22	23	45	55	36	23							

* Showing on which day each of the 7 cortisol determinations was made.

TABLE V
Blood Cortisol Level ($\mu\text{g./100 ml.}$) in 13 Healthy Subjects

Test Arrangement*														
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Determination No. ..	1	2						3	4 (ACTH)	5 (ACTH)	6	7		
Subject No.	Determination No.													
	1	2	3	4	5	6	7							
1	22	22	21	60	86	75	—							
2	21	21	20	55	82	71	—							
3	12	13	—	53	65	39	11							
4	11	14	13	35	43	65	10							
5	18	18	20	51	70	48	—							
6	18	12	12	44	45	28	14							
7	11	15	13	64	92	60	18							
8	15	15	16	34	37	41	20							
9	16	14	18	47	58	48	16							
10	17	16	17	57	81	—	13							
11	17	10	12	65	71	69	17							
12	16	17	13	45	81	—	19							
13	12	12	12	29	39	21	8							

* Showing on which day each of the 7 cortisol determinations was made.

TABLE VI
Response to ACTH, Scheffé Test

Result of first dose of ACTH	Healthy	Not Treated with Corticosteroids	Normal Blood Cortisol Level During Treatment	Decreased Blood Cortisol Level During Treatment
Result of second dose of ACTH				
Healthy		s	s	s
Not treated with corticosteroids ..	n.s.		n.s.	s
Normal blood cortisol level during treatment ..	s	s		s
Decreased blood cortisol level during treatment ..	n.s.	n.s.	n.s.	

s = significant at the 5% level.
n.s. = not significant at the 5% level.

with steroids and exhibiting a normal blood cortisol level during treatment.

(3) There was no significant difference between the increases recorded in the two categories of patients treated with steroids.

While the SD of the individual observation in the

normal range was 3 $\mu\text{g./100 ml.}$ (see above), in the range attained in the steroid-treated patients after administration of ACTH, the SD of the individual observation will differ from the corresponding mean for the population by at most 2 SD with a probability of 95%, the appropriate value for SD can be used as a guide in interpreting any particular test result in steroid-treated patients.

Comparison of Various Groups of Test Subjects

The various groups of patients have been compared with one another as regards: data, history, allergy, pulmonary function, and treatment with steroids (Tables I and II).

Investigations concerning allergy and pulmonary function have rarely been carried out simultaneously with the study of the hypophyseo-adrenal function. However, in nearly all cases the study of pulmonary function was carried out not more than 6 months before or after the study of hypophyseo-adrenal function, and if possible during a clinically quiescent phase.

The various groups did not differ from one another in age composition. Only a few of the children had reached puberty. The mean ages of onset of the first symptoms of asthma, and the numbers of years that asthma had been present corresponded closely. As was to be expected, the asthma patients not treated with steroids experienced more symp-

TABLE VII
Duration of Corticosteroid Treatment

No. of Months of Treatment	0-12	13-24	25 or Longer	Average
Normal blood cortisol level during treatment (n = 12) ..	4	6	2	18
Decreased blood cortisol level during treatment (n = 13) ..	2	4	7	24

TABLE VIII
Total Dose of Corticosteroids Received

	Mean Quantity of Cortisone Equivalent Used per 18 Months of Treatment (mg.)*	Mean Quantity of Cortisone Equivalent Used per m. ² /24 Hours During the Last 6 Months of Treatment (mg.)
Normal blood cortisol level during treatment (n = 12) ..	8300	14.3†
Decreased blood cortisol level during treatment (n = 13) ..	10300	18.0

* Rounded off to nearest hundred. † If Case No. 21 is disregarded: 12.4.

toms during the period preceding investigation than those who had been so treated. If, in the steroid-treated groups, we compare the categories *normal blood cortisol level during treatment* and *decreased blood cortisol level during treatment*, we find that they are similar as regards the frequency and duration of the attacks of breathlessness, and the symptoms occurring during the attack-free intervals. The majority of the patients gave a positive skin reaction to house dust, and many gave a positive reaction to moulds and pollen.

There were no significant differences between the various groups as regards the degree of derangement of expiration. Inspiration was more commonly normal in the asthma patients not treated with steroids than in those treated. In all the groups, only a minority presented a disordered function which was irreversible or incompletely reversible, but a few patients exhibited abnormal elasticity characteristics or an increased dead-space effect.

In Table VII the duration of treatment with steroids is detailed, and in Table VIII details of dosage.

The group with decreased blood cortisol level during treatment had on the average been treated

longer and with a higher dose of steroids than the group with normal blood cortisol level during treatment. The figures shown in the second column of Table VIII show a significant difference at the 5% level if tested one-sided against the alternative hypothesis, that the mean quantity of cortisone equivalent used is greater in those with a decreased blood cortisol level than in those with normal blood cortisol level during treatment (test of Wilcoxon).

Discussion

In children, the determination of the blood cortisol level is preferable to determination of the urinary 17-hydroxycorticosteroids. Technically it is simple and quantitative urine collection is avoided. The figures obtained show so little fluctuation that they presumably reflect the hormonal situation with great reliability.

In 3 children with a normal blood cortisol level during treatment, the examination was carried out twice at an interval of 1-1½ years. The results of these tests are in close agreement with one another (Table IX), and indicate the satisfactory reproducibility of the test.

TABLE IX
Reproducibility of ACTH Test (Robinson)

Patient No.	Determination No.*							
	1	2	3	4	5	6	7	8
18 { I	17	13	10	8	45	48	20	18
{ II	18	16	12	24	35	52	23	20
19 { I	14	11	14	13	36	44	18	13
{ II	17	11	12	16	33	44	20	20
9 { I	3	13	12	8	20	29	29	10
{ II	3	8	12	13	23	38	36	11

* For test arrangement: see Table III.

FIG. 2.—Blood cortisol level in 3 children with asthma treated with corticosteroids; comparison with group with decreased blood cortisol level during treatment. $\bar{x}$ = mean $\pm$ 2 SD of group with decreased blood cortisol level during treatment; $\times$ = patient G.V.; $\circ$ = patient D.T.; Δ = patient J.K.

Symptoms of insufficiency of the adrenal cortex after discontinuing steroid treatment have not been observed in any subjects. Although most patients had more asthma symptoms after stopping steroids, these symptoms were never very severe, probably in part because of the ACTH administered.

In the patients with decreased blood cortisol level during treatment, this level rose within 48 to 72 hours of stopping treatment to a level that did not differ from that recorded in the other groups. This is a normal response, according to Robinson *et al.* (1962). In these patients, therefore, after steroid therapy was discontinued, the hypophysis and the adrenal cortex produced sufficient ACTH and cortisol to fulfil normal physiological needs.

However, the work of others indicates that after maximal stimulation of the adrenal cortex with ACTH, the subjects in this category do show a decreased response, both the actual and the potential cortisol reserve being depressed (Renold, Jenkins, Forsham, and Thorn, 1952).

Whether this also holds good with respect to the pituitary as well as to the adrenal cortex reserve we have been unable to establish. The results of studies of inhibiting ACTH production by the administration of corticosteroids are equivocal (Danowski, Bonessi, Sabeh, Sutton, Webster, and Sarver, 1964; Graber, Ney, Nicholson, Island, and Liddle, 1965). If blood ACTH levels cannot be determined, it is necessary to resort to an indirect method such as the vasopressin test (Gwinup, 1965; Landon, James, and Stoker, 1965; van der Wal *et al.*, 1965). It has been stated that administration of

lysine-vasopressin can lead to stimulation of the adrenal cortex by inducing release of ACTH from the hypophysis, with resulting rise in blood cortisol level. However, there is some doubt as to whether this stimulation takes place exclusively via ACTH (Hilton, Scian, Westermann, Nakano, and Kruesi, 1960).

In three asthma patients (not listed in Table III) there was no increase in blood cortisol level—decreased during steroid treatment—after discontinuation of steroids (Fig. 2). Maximal stimulation of the adrenal cortex in two subjects (J.K. and D.T.) caused only minimal increase in the blood cortisol level, and in a third (G.V.) an increase that was within the range of scatter of the category decreased during treatment. In J.K. and D.T. it appears probable that considerable atrophy of the adrenal resulted from the treatment. Patient J.K. had been continuously treated with prednisolone or betamethasone for 57 months. Since initially he was treated elsewhere, the total quantity of corticosteroids administered to him is unknown. During the 6 months before the test he was given betamethasone 0.6 mg./m.² 24 hours (equivalent to 20 mg. cortisone). As regards patient D.T., no precise data concerning the duration and the dosage of the treatment are known. However, the treatment has been maintained for more than 4 years. Patient G.V. has been treated with prednisolone and betamethasone for 16 months. During the 6 months before the test, he was given betamethasone 0.6 mg./m.² 24 hours.

It is interesting to note that even in these patients

no symptoms of adrenocortical insufficiency occurred after the treatment was stopped.

These facts suggest that where a blood cortisol level that is decreased during the administration of steroids fails to return to normal after steroids are discontinued, there may exist an almost non-responsive adrenal cortex.

If the blood cortisol level is normal during treatment, no rise will take place after its withdrawal. Furthermore, with maximal stimulation of the adrenal cortex with ACTH it can be shown that in these patients the actual cortisol reserve is also adequate, being no less than in asthmatic children not treated with steroids, but who are comparable in age, number of years of asthma, and pulmonary function. The potential cortisol reserve, on the other hand, is lower.

The clinical importance of decreased function of the hypophyseo-adrenocortical system is the risk of sudden functional inadequacy during stress (trauma, operation, infection, etc.). A number of well-documented cases of this type have been reported (Fraser, Preuss, and Bigford, 1952; Salassa, Bennett, Keating, and Sprague, 1953; Bayliss, 1958; Sampson, Brooke, and Winstone, 1961; Robinson *et al.*, 1962).

Whether the reserve capacity of the hypophyseo-adrenocortical system will be adequate in any given situation will always depend on the nature and the duration of the stress. This element cannot be assessed experimentally with a 'stress test'. Pyrogens, and hypoglycaemia after administration of insulin, provide only a brief and moderate stimulus, the effects of which are variable and difficult to standardize. As mentioned, the fact that a blood cortisol level which has been decreased during treatment returns to normal within 48-72 hours of the treatment being stopped does not necessarily mean that the adrenal cortex will respond normally to a maximal stimulation by means of ACTH. Although the possibility of insufficiency of the hypophyseo-adrenocortical system during stress arises, in many cases the adrenals still appear in practice to retain a reasonable reserve capacity.

Our present results lead to the following conclusions. If a blood cortisol level that is decreased in the course of the therapy fails to rise after it is stopped, then should additional demands be subsequently made on the hypophyseo-adrenocortical system, this system may well prove insufficient.

If the blood cortisol level remains normal during treatment, the production of ACTH by the hypophysis is not severely affected and the reserve capacity of the adrenal cortex will have decreased

only slightly. The danger of insufficiency of the hypophyseo-adrenocortical system may, therefore, in these cases be regarded as slight. Provided the blood sampling for cortisol level has been made under basal circumstances, the result will reliably indicate the situation.

It is, therefore, advisable that children who are being treated with steroids should be submitted occasionally to a determination of blood cortisol level (e.g. once every 3 to 6 months). This must be done under basal conditions, early in the morning (fasting, bed-rest, 8 a.m., absence of infections, trauma, or other stress). In the case of out-patients, this implies that the blood samples will have to be taken at home.

If in the course of therapy a decreased value is encountered, the Robinson test can be performed in order to gain some impression as to whether or not the hypophyseo-adrenocortical system is functioning. For this, the patients should be in hospital. If a dubiously decreased value is found, the examination should be repeated after a short interval, but this should be rare (see Table X).

TABLE X

Blood Cortisol Level During Treatment With Corticosteroids (52 patients)

No.	Cortisol Level (μ g./100 ml.)		
	≤ 6	7-9	> 9
	21	8	23

Shuster and Williams (1961), studying adult subjects (approx. 2 m.²) with rheumatoid arthritis, observed that the adrenal cortex always responded normally to ACTH if protracted steroid treatment had not exceeded 20 mg. cortisone equivalent per day, while the response was always decreased if the dosage had been 30 mg. or more of cortisone equivalent per day. This is more or less in agreement with our own findings (Table VIII). The 24-hour production under normal conditions amounts to 10-20 mg. hydrocortisone per m.² (Kenny, Malvaux, and Migeon, 1963).

Treadwell, Savage, Sever, and Copeman (1963) have reported that the duration of the treatment and the total amount of corticosteroids used show a correlation with the degree of inhibition of the hypophyseo-adrenocortical system. The observations made in the cases of patients J.K. and D.T. (Fig. 2) are in agreement with this conclusion, and the figures in Table VII point in the same direction.

From the findings obtained, no close relation between the duration of the treatment and the dosage on the one hand and the degree of inhibition of the hypophyseo-adrenocortical system on the other can be deduced. The assumption appears to be justified, however, that there is little objection to the administration of prednisolone 3 mg./m.² 24 hours for a period somewhat in excess of a year.

Summary

With the aid of the Robinson test in combination with the ACTH test, a study was made of the function of the hypophyseo-adrenocortical system in healthy children and in children suffering from asthma, of whom some had and others had not been treated with corticosteroids.

If in the course of treatment with corticosteroids a normal blood cortisol level is found, it may be assumed that there is no significant impairment of the hypophyseo-adrenocortical system. If in the course of treatment with corticosteroids the blood cortisol level is decreased (≤ 6 μ g./100 ml.), the system is inhibited; by means of the combination of tests used in this investigation the degree of such inhibition can be deduced.

There was no close correlation between the duration or dosage level of corticosteroid treatment, and the degree of inhibition of the hypophyseo-adrenocortical system, though some information on this relationship was obtained.

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