Effect on Height of Corticosteroid Therapy in Asthmatic Children*

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The daily administration of corticosteroids to children may result in a retardation of height as well as of skeletal maturation (Blodgett *et al.*, 1956; van Metre and Pinkerton, 1959; Falliers *et al.*, 1963). The physiology of this phenomenon is unknown: corticosteroids influence the structure and development of bone (Laron, 1966a), while the production of growth hormone may also be impaired (Frantz and Rabkin, 1964; Hartog, Gaafar, and Fraser, 1964).

The degree of growth inhibition correlates with the nature and dosage of the corticosteroid used, cortisone being said to cause the least retardation of growth; daily doses to a maximum of approximately 50 mg./sq. m. having no influence on the rate of increase of height. The same is said to be true of prednisone in a daily dose of 6 mg./sq. m. (therapeutically equivalent to 24 mg. cortisone). Beta-methasone is reported to cause retardation of growth in daily doses of 0.6 mg./sq. m. (equivalent to 24 mg. cortisone) or more (Blodgett *et al.*, 1956; van Metre, Niermann, and Rosen, 1960; Falliers *et al.*, 1963).

It is usually assumed that height growth and skeletal maturation are affected to the same degree. This implies that growth inhibition caused by the steroids does not necessarily lead to a decrease in adult height, provided the catch-up growth that occurs after the termination of the treatment (Prader, Tanner, and von Harnack, 1963) is not less for height than for skeletal maturation. The number of observations on this point is small (Laron, 1966b).

This paper reports the results of investigations

into: (1) corticosteroid dosage and height growth; (2) corticosteroid therapy and the relation of height growth and skeletal maturation; (3) the course of catch-up growth of height and skeletal maturity after discontinuing corticosteroid treatment.

Patients, Methods, and Criteria

Severity of asthmatic symptoms and the failure to relieve them with measures other than steroids formed the principal indication for treatment with steroids. Detailed clinical and laboratory data on many patients have been published elsewhere (Kerrebijn, de Kroon, and Harders, 1967a; Kerrebijn *et al.*, 1967b). The children were examined as outpatients every 4 to 6 weeks. During each examination, the dosage for the next period was determined on the basis of the symptoms of the previous period. The dosage often varied therefore, the aim being to keep it as low as possible. Complete absence of complaints or symptoms was not necessarily attempted. Steroid therapy was always combined with bronchodilator drugs and, if necessary, with antibiotics, and with physical and psychological therapy.

At each examination the patients were weighed and measured, height being measured according to a standardized procedure (Marshall, 1966), with a wall measure to an accuracy of 0.1 cm.

Once every 6 months the skeletal age of the left hand was determined by the method of Tanner, Whitehouse, and Healy (1962).

Analysis of the growth data was carried out only for those children who had been treated daily with prednis-(ol)one for at least 6 months.

The children showed no external signs of sexual maturation, and had a skeletal age of 6.0–10.0 years. On average the increase in height of normal boys and girls who fulfil both criteria amounts to 5 to 6 cm. per year.

For each child the following data were collected for each period between two measurements of stature:

(1) The height growth during this period (ranging from 4–16 weeks), expressed in cm. per year.

Received March 6, 1968.

*This investigation was made possible by a grant from the "Nederlands Astma Fonds".

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TABLE I

Dosage of Prednis(ol)one and Height Growth in Boys and Girls without External Signs of Sexual Maturity and with Bone Age of 6.0–10.0 years (Tanner)

Daily Dosage Prednis(ol)one/sq. m.						
Case No.	0.1–2.9 mg.†		3.0–3.9 mg.†		4.0–5.9 mg.†	
	Average Increase in Height (mm./wk.)	No. of Weeks*	Average Increase in Height (mm./wk.)	No. of Weeks*	Average Increase in Height (mm./wk.)	No. of Weeks*
1	1.1	14	0.0	22	–0.5	10
2	1.4	40	2.5	6	0.1	50
3	0.7	42	1.0	26	0.3	117
4	0.8	64	0.4	37	1.1	31
5	1.2	9	1.7	12	0.4	69
6	0.6	63	–0.8	6	1.0	26
7	0.8	44	0.0	5	1.0	26
8	0.9	16	0.0	12	0.6	35
9	0.8	26	0.8	12	0.2	40
10	1.5	10	0.4	14	0.3	62
11	1.4	22	1.0	24	0.0	6
12	1.3	16	0.0	19	0.3	88
13	1.7	26	0.8	6	0.8	26
14	0.6	52	0.0	6	0.6	36
15	1.1	84	0.3	30	1.2	4
16	1.3	31	1.6	34	0.3	98
17	0.6	24	3.1	8	0.4	81
Mean	1.0 i.e. about 5.0 cm. per year		0.7 i.e. about 3.5 cm. per year		0.4 i.e. about 2.0 cm. per year	

* This column indicates the total number of weeks during which the dosage mentioned in the heading of the columns was administered. As a rule, this figure is the sum of a number of shorter periods during which other doses were administered. The minimal number of weeks between two measurements was 4.

† Body surface in an 8-year-old child of average height and weight is approximately 0.9 sq. m.; in a 9-year-old 1.0 sq. m.; in a 10-year-old 1.1 sq. m. A daily dosage of 4.5 mg./sq. m. in an average 10-year-old means a daily amount of 5 mg.

(2) The daily dose of steroid per sq. m. body surface. This dosage is subdivided into 3 groups: (a) 0.1–2.9 mg. prednis(ol)one/sq. m. per 24 hr. (equivalent to 0.4–12 mg. cortisol), i.e. less than the equivalent daily normal quantity of hydrocortisone produced by the adrenal glands (Kenny, Malvaux, and Migeon, 1963); (b) 3.0–3.9 mg. prednis(ol)one/sq. m. per 24 hr. (equivalent to 12–16 mg. cortisol), i.e. corresponding to the daily normal quantity of hydrocortisone produced by the adrenal glands; and (c) 4.0–5.9 mg. prednis(ol)one/sq. m. per 24 hr. (equivalent to 16–20 mg. cortisol), i.e. more than the equivalent daily normal quantity of hydrocortisone produced by the adrenal glands.

Results

Dosage of prednis(ol)one and height growth.

Table I gives for each of 17 children the mean height increment for each of the three dosage groups. Growth data at the beginning of the treatment are given in Table II.

If the method of variance analysis is applied to the data in Table I, there are between the dosage groups significant differences with regard to the mean height growth ($p < 0.01$). In this analysis, every observation was weighted with reference to

the number of weeks on which it was based, so that the influence of observations over a short period was slight. In addition, a correction was applied for the differences in individual height growth of children from Table I.

The mean increase in height for the group receiving the smallest dosage is hardly less than normal; that for the group receiving the largest dosage is considerably less than normal.

Prednis(ol)one treatment, and relation of height growth and skeletal maturation. The effect of steroid dosage on skeletal maturity has been studied by investigating the relation between height growth and skeletal maturity.

An increase in height of 1 cm. corresponds on average to an advance in skeletal age of a certain number of months. This number depends on the age. In the children listed in Tables I and II, a mean increase in height of 5.5 cm. per 12 months of skeletal age would be expected, assuming that skeletal age increases 12 months per year in a population of this age.

The following equation applies on average to

TABLE II
Growth Data of Children Listed in Table I at Beginning of Prednis(ol)one Treatment

Case No.	Sex	Chronological Age (yr.)	Bone Age (yr.) (Tanner, Whitehouse, and Takaishi, 1966)	Height		
				cm.	Centiles in Relation to Chron. Age	Centiles in Relation to Bone Age
1	M	8.3	8.0	135.0	90	95
2	M	7.3	8.1	123.5	60	25
3	M	8.3	8.7	126.5	50	25
4	M	9.3	8.5	139.5	80	97
5	M	7.8	7.9	127.0	80	50
6	M	9.9	9.8	136.5	50	50
7	M	9.4	10.0	135.5	70	40
8	M	9.2	9.6	144.0	97	95
9	M	9.6	9.7	133.5	40	40
10	M	10.5	9.6	139.5	50	75
11	M	5.6	6.3	114.0	75	30
12	M	10.5	9.7	144.5	75	95
13	F	6.6	6.4	122.0	80	90
14	F	9.7	9.3	134.0	50	70
15	F	9.3	9.8	131.5	50	25
16	F	8.1	9.2	126.0	50	20
17	F	7.2	8.5	124.0	75	25

these children (cf. Tanner and Whitehouse, 1967):

$$b = \frac{\text{increase of skeletal age in 'years' per year}}{\text{increase in height in cm. per year}} = \frac{1}{5.5} = 0.18 \text{ 'years' per cm.}$$

The value of b has been estimated for 14 of the 17 children listed in Table I, with the aid of regression calculations from the data concerning height and skeletal age. In the remaining 3 children the

skeletal age had been determined less than 4 times. The values of b are listed in Table III, which also lists the number of pairs of observations of height and skeletal age (n); the estimated standard error of the coefficient b (s_b);* and the estimated standard deviation of the difference between the skeletal age observed and the skeletal age that might be expected on the basis of the height(s).

From this Table the following statistical conclusions can be deduced: (1) Both with regard to the level b and to the deviation s , there are differences between the children. (2) The values of b listed in Table III are (as a whole) significantly lower ($p=0.01$; sign test) than would have been expected on the basis of the hypothesis that on the average $b = 0.18$, suggesting that in the children treated with prednis(ol)one skeletal maturation is retarded with respect to height growth.

Catch-up growth after discontinuation of prednis(ol)one treatment. Treatment with steroids may cause a child to deviate from a particular growth centile, as noted above. We have attempted to estimate the acceleration of growth after discontinuing treatment ('catch-up growth') in a number of prepubertal children in order to make sure that the acceleration was not a consequence of androgen or oestrogen action.

As already mentioned, the mean annual height increment (50th centile of the curve of the growth

TABLE III

Increase in Height and Skeletal Maturation*

Case No.	n	b	s_b	s
2	5	0.10	0.03	0.20
3	6	0.13	0.02	0.25
4	7	0.24	0.03	0.33
5	5	0.12	0.01	0.05
6	6	0.09	0.02	0.17
7	5	0.05	0.00	0.01
9	5	0.07	0.01	0.02
10	5	0.05	0.01	0.05
11	6	0.17	0.02	0.24
13	6	0.11	0.01	0.15
14	7	0.18	0.02	0.18
15	6	0.09	0.01	0.18
16	7	0.13	0.02	0.15
17	6	0.14	0.03	0.23
Mean		0.12	0.02	0.16

n = number of pairs of observations of height and skeletal maturation

$$b = \frac{\text{increase of skeletal age in 'years' per year}}{\text{increase in height in cm. per year}}$$

s_b = standard error of b

s = standard deviation of the difference between the actual and the expected bone-age.

* For most children the time taken to collect these data has been longer than that for the data in Table I.

* The meaning of s_b can be explained by the following example: In Table III we find for Case 3: $b = 0.13$ and $s_b = 0.02$ in 6 observations. With the aid of these values it can be calculated that over the observation period the real value of b lies between 0.07 and 0.2, with a confidence of 95%.

rate) for boys and girls at the range of ages considered, is about 5 to 6 cm.

The number of prepubertal children with adequate data of catch-up growth was small, so that it was not possible to determine whether the course of catch-up growth presented any particular pattern. An impression, however, could be obtained (see Table IV). In the 6 children examined, the catch-up growth was slow: 12 months after discontinuing steroid therapy only one of them (Case 20) had reached the height level that might have been expected without this therapy. In Case 19, this level had almost been reached after 20 months, but no follow-up was possible after this stage. Case 18 had reached it after 20 months.

The degree of catch-up growth appeared variable. It may depend in part on the duration of the treatment and on the dosage, but this could not be determined in our small sample.

Eight children from the Asthma Centre 'Bosch en Heide', who, according to age and maturation characteristics, were comparable to our children and who had been treated with steroids for more than 6 months, showed during the first 12 months after discontinuing steroid treatment an increase in height of the same degree as the children listed in Table IV* (Table V).

The value of the quotient 'b' has also been estimated for the catch-up growth. In 4 out of 5 children during the first 12 months after discontinuation of treatment the height increased relatively more than the skeletal age (Table IV). This would in part be caused by the fact that skeletal maturity lags behind. A larger number of observations over a longer period would be necessary to justify such a conclusion.

Discussion

Some possible sources of error may first be considered. If a child was having an attack of asthma at the time of measuring, it was not always possible for the back, usually curved at such a time, to be straightened sufficiently for the measurement to reflect the height accurately, and the resulting errors could not be entirely avoided. They may well have been the cause of the 'negative' height increment that has been recorded in a few instances (see Table I).

Another source of error might be that, in analysing the findings, the seasons during which the height growth had occurred have not been taken into account.

It is possible that larger doses of corticosteroids might be given during one particular season (e.g. in

autumn, when the symptoms of asthma are often more severe). If this season were to coincide with that when the natural height growth is minimal (opinions are divided regarding this aspect, see de Wijn and Postmus, 1966), the differences in height growth after different doses of steroid might not be attributed solely to these differences of dosage.

Applying Friedman's test of m-rankings (for each child the four seasons are ranked in the order of the mean dosage) shows no consistent differences between seasons with regard to the dosages of steroids prescribed.

The doses listed in Table I are the prescribed doses. It is possible that the dose prescribed was not always the same as the quantity actually taken. However, the correlation encountered between the height growth and the dosage prescribed justifies the conjecture that the patients usually followed the dosage regimen and this is supported by the fact that the children included in the investigation attended with their parents conscientiously.

Certain authors (Falliers *et al.*, 1961; Schook, 1966) believe that children with severe asthma are on the average smaller than normal, irrespective of any effect of steroid therapy; others (van Metre and Pinkerton, 1959; Spock, 1965) have not found this. These different findings may be due to groups of patients of different authors not being uniform with regard to the nature and the severity of the disease.

We consider that corticosteroids are the main cause of growth impairment. Asthmatic symptoms may be partly responsible too, but their influence seems not to be great, because we observed no difference between the growth pattern during symptom-free and non-symptom-free phases (Kerrebijn *et al.*, 1967b).

It is possible that a given dosage of prednisone may impair growth more in prepubertal than in pubertal children. For instance, during puberty there are high levels of androgens or oestrogens that may wholly or partially suppress the inhibitory effect of the corticosteroids.

The dosage of prednisone with which Falliers *et al.* (1963) found no impairment of growth (6 mg./sq. m. per 24 hr.) did show an inhibitory effect on height growth in the present investigation in prepubertal children. Falliers *et al.* only mention the age range (6–16 yr.), but not the age distribution or the maturity distribution of their children investigated, so that the difference might be due to a difference in maturation between the children examined by them and those examined by us.

The relation between the degree of growth impairment and the dosage of prednisone in prepubertal children shows that the risk of growth

* We are indebted to Dr. C. F. Schüller for permitting us to quote these data.

TABLE
Catch-up Growth after Discontinuing

Case No.	Sex	Starting Treatment				End of Treatment	
		Age (yr.)	Bone Age (yr.)	Height		Duration of Treatment (mth.)	Age (yr.)
				cm.	Centiles		
22	M	8.4	8.0	125.5	30	18	9.9
12	M	10.5	9.7	144.5	75	29	12.8
18	F	6.5	5.9	113.5	30	25	8.5
19	F	7.3	8.2	120.0	40	34	10.1
20	M	10.4	8.3	139.0	50	13	11.4
21	M	7.9	7.9	127.0	70	12	8.9

TABLE V
Height Growth (cm.) During 12 Months after Discontinuing Steroid Treatment (prepubertal children)

Juliana Children's Hospital*		Astma Centre 'Bosch en Heide'†	
Case No.	Growth (cm.)	Case No.	Growth (cm.)
22	7.0	23	6.0
12	6.5	24	7.5
18	8.0	25	6.0
19	8.0	26	7.5
20	7.0	27	7.0
		28	7.5
		29	7.0
		30	8.5

* For age and bone age: see text.

† Age and bone age comparable to children of first column.

impairment is small when the dosage is below the equivalent amount of hydrocortisone produced by the adrenal.

If this dosage is exceeded, the risk of impairment

TABLE VI A
Puberty and Bone Age in Girls Treated with Prednis(ol)one

Case No.	Age of Menarche* (yr.)	Corresponding Bone Age (yr.) (Tanner)†	Duration of Treatment (mth.)
31	14.0	12.2	50
32	14.5	12.3	16
33	13.7	12.7	31
34	13.7	12.2	81
35	13.2	13.6	15
36	12.6	12.6	13
37‡	15.6	14.2	24

* In 26 normal girls: 11.2–18.1 years (av. 13.4) (H. H. Van Gelderen, 1967, unpublished data).

† In 19 normal girls: 12.6–13.7 years (av. 13.3) (H. H. Van Gelderen, 1967, unpublished data).

‡ Severe bronchiectasis.

of height growth is great*. The same applies to the impairment of the hypophyseo-adrenocortical system (Kerrebijn *et al.*, 1967a).

The correlation shown between the increase in height and the skeletal maturation before puberty indicates that skeletal maturation lags behind during steroid treatment. This, and the facts concerning catch-up growth after stopping treatment, make it unlikely that steroid treatment, unless very prolonged, reduces final adult height.

As a rule, a considerable time must elapse after discontinuing treatment before the child reaches his original growth centile. More data need to be collected on this point, and would require the co-operation of several centres.

External signs of sexual maturation are closely correlated with bone age. Retardation of skeletal maturation in the course of steroid therapy probably does not involve retardation of puberty.

TABLE VI B
Puberty and Bone Age in Boys Treated with Prednis(ol)one

Case No.	Age of First Measurement of Testicular Volume ≥ 5 ml. (yr.)*	Corresponding Bone Age (yr.) (Tanner)†	Duration of Treatment (mth.)
38	12.2	11.4	63
39	14.1	11.6	40
40	14.0	13.0	23
41	14.9	12.4	35
42	14.0	12.7	42
43	13.4	14.0	15

* In 26 normal boys: 12.0–17.0 years (av. 14.5) (H. H. Van Gelderen, 1967, unpublished data).

† In 26 normal boys: 12.0–14.8 years (av. 13.4) (H. H. Van Gelderen, 1967, unpublished data).

* The finding that on the whole a higher dosage gives more growth impairment does of course not mean that this applies to each child in the same way.

IV Treatment (prepubertal children)

Treatment			End of Catch-up Period				Increase of Skeletal Age (yr.)
Bone Age (yr.)	Height		Duration (mth.)	Bone Age (yr.)	Height		Increase in Height (cm.)
	cm.	Centiles			cm.	Centiles	
9.6	129.5	15	12	10.4	136.5	25	0.11
10.1	151.0	50	12	10.8	157.5	50	0.12
7.2	121.5	10	12	8.3	129.5	25	0.14
9.0	131.5	20	12	10.2	139.5	30	0.16
9.0	142.5	35	12	10.7	149.5	50	0.24
8.4	129.0	40	6	—	134.0	50	—

In 7 girls and 6 boys, who were treated continually for more than 1 year, with an average daily dose of 4.0–5.9 mg./m.² prednis(ol)one, bone age has been measured at the age of menarche, or at the age when testicular volume reached 5 ml. (Tables VIA and VIB) (This indicates the beginning of puberty in boys, Dooren, van Gelderen, and Hamming, 1963.) The chronological age at which menarche occurred averaged 13.5 years (except Case 37), about the same as in normal girls. The bone age at this time averaged 12.6 years, a little less than normal controls. In boys, the chronological age at which testicular volume reached 5 ml. was 13.7 years, and the corresponding bone age averaged 12.6 years. Both are less than normal controls. It seems, therefore, that when skeletal maturation lags behind, sexual maturation does not do so.

Summary

Height, skeletal maturation, and puberty in children with asthma who were treated with prednis(ol)one were studied.

In prepubertal children the risk of growth impairment is small if the daily prednis(ol)one dosage is less than 3 mg./sq. m. If it is more than 4 mg./sq. m. the risk of growth impairment is great.

Skeletal maturation tends to be retarded more than height during steroid treatment.

Catch-up growth after discontinuing treatment is slow and variable.

Onset of puberty was normal in the children investigated, in spite of retardation of bone age.

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