

# Growth and skeletal maturation in congenital adrenal hyperplasia

## Review of 20 cases

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**Bailey, C. C., and Komrower, G. M. (1974).** *Archives of Disease in Childhood*, **49**, 4. **Growth and skeletal maturation in congenital adrenal hyperplasia: review of 20 cases.** In 20 children with the salt-losing variety of congenital adrenal hyperplasia there was a significant degree of stunting and their skeletal maturation was delayed. 14 of the children were treated in the first year of life with long-acting steroid preparations and 13 of this group achieved normal height velocities during this period. Treatment thereafter was with prednisone and 9- $\alpha$ -fludrocortisone, and it is concluded that the growth retardation of the children was due either to a specific effect of these drugs, or to drug overdosage.

Growth patterns in children with the salt-losing variety of congenital adrenal hyperplasia have been studied by various authors (Bergstrand, 1966; Laron and Pertzelan, 1968; Rappaport, Cornu, and Royer, 1968; Sperling *et al.*, 1971; Stempfel *et al.*, 1968). Most investigators have found that there is a growth failure in this group of children related to the growth retarding effects of the steroid therapy which they have received (Raiti and Newns, 1970).

In an attempt to prevent such growth failure, various treatment schedules have been recommended (Bergstrand, 1966; Blodgett *et al.*, 1956; Laron and Pertzelan, 1968; Migeon, 1968; Rappaport *et al.*, 1968; Sperling *et al.*, 1971; Stempfel *et al.*, 1968). The optimal dosage of steroid for pituitary suppression with minimal growth inhibition that has been recommended varies from 30 to 40 mg hydrocortisone/m<sup>2</sup> per day by Sperling *et al.* (1971) to 12 to 36 mg by Migeon (1968).

In the first year of life regular administration of an oral steroid preparation presents difficulties such as vomiting and refusal to take the preparation, and frequent intramuscular injections are painful and time consuming. Long-acting steroid preparations given by intramuscular injection at monthly intervals have been used in an attempt to avoid these problems. However, various series have been reported in which the long-acting hormone preparations have been shown to have more growth

inhibiting effect than hydrocortisone (Laron and Pertzelan, 1968; Stempfel *et al.*, 1968). Laron and Pertzelan reviewed the growth of 6 children who had been treated interchangeably with 6- $\alpha$ -methylprednisolone, 6- $\alpha$ -fluprednisolone, and hydrocortisone. They found that in this group hydrocortisone permitted normal linear growth while 6- $\alpha$ -methyl- and 6- $\alpha$ -fluprednisolone both caused growth retardation. Stempfel *et al.* studied pituitary growth hormone secretion in 7 patients who received 6- $\alpha$ -methylprednisolone. They found that the normal response to insulin-induced hypoglycaemia was depressed in these patients, and that it was restored by changing their therapy to hydrocortisone. Vazquez, Schutt-Aine, and Kenny (1972) studying a child treated with intramuscular and oral cortisone, and Sturge *et al.* (1970) studying children treated with prednisolone, did not find any growth hormone suppression in their patients.

### Patients and methods

The group consisted of 16 girls and 4 boys. Their ages at the time of the survey ranged from 1 year 6 months to 17 years 4 months. Therapy had started in the first month of life in 17 cases, at 3 months in 2 cases, and at 8½ months in 1. With the exception of 4 children who were diagnosed at other centres, the condition was first brought under control using short-acting preparations of deoxycorticosterone acetate (DOCA) and hydrocortisone, and then was continued by using

implants of DOCA placed into either the anterior abdominal wall or, more recently, into the interscapular space. Glucocorticoid was given as intramuscular injections of prednisone tri-methyl acetate (PTMA) at 3- to 5-weekly intervals. When the patients were old enough to be given oral therapy reliably they were treated with prednisone and 9- $\alpha$ -fludrocortisone. Dexamethasone was used for a short period in 3 cases, and methylprednisone acetate (Depo-Medrone) in 1 case.

Extra salt was given in the diet to all patients, usually in a daily dosage of 2 g during the first year of life.

Therapy was regulated by measuring the 24-hour urinary output of  $\Delta$ -5-pregnanetriol and 17-oxosteroid. An output of not more than 0.5 mg/24 hr of  $\Delta$ -5-pregnanetriol was taken as a satisfactory level of control. The 17-oxosteroid output increases with age, and figures of <0.5 mg/24 hr under 1 year of age, <1.5 mg under 4 years of age, <2.5 mg thereafter have been accepted as satisfactory. Higher levels may have been permitted for a short time in order to assess the significance of a single high urinary level by repeating it a month later. The urinary sodium excretion and urine volume was measured at the same time as the steroid levels and gave an indication of the adequacy or otherwise of mineralocorticoid replacement. A sodium output of 200 mEq/24 hr was taken as an adequate level of control.

The children were measured at each hospital visit on a stadiometer and height was plotted on centile charts for linear growth and height velocity as prepared by Tanner and Whitehouse. Skeletal age was assessed at 12-month intervals on a wrist x-ray using the standards of Greulich and Pyle.

### Results

Fig. 1 and 2 illustrate the height and skeletal age of each child plotted against chronological age at the time of the survey. The open square represents the skeletal age of the child in years and relates only to the horizontal axis of the diagram and not to the centile lines. All the children are on or below the 25th centile. 7 are on or below the 10th centile, and 11 are on or below the 3rd centile. There is, therefore, a significant degree of stunting in the group.

The skeletal age of the children in this group is similarly retarded with respect to chronological age, i.e. there is a disparity of 6 months or more in 13 out of the 20 children. Skeletal age is equivalent to chronological age in 4 children and is in advance in 3 children.

It is of interest to note that in the 11 children who are below the 3rd centile for height, skeletal age is retarded in 9.

An attempt has been made to relate these findings to the therapy which this group of children received in the first year of life, as it is in this respect that they differ from most other groups so far reported. 14 children received PTMA and all except one of these

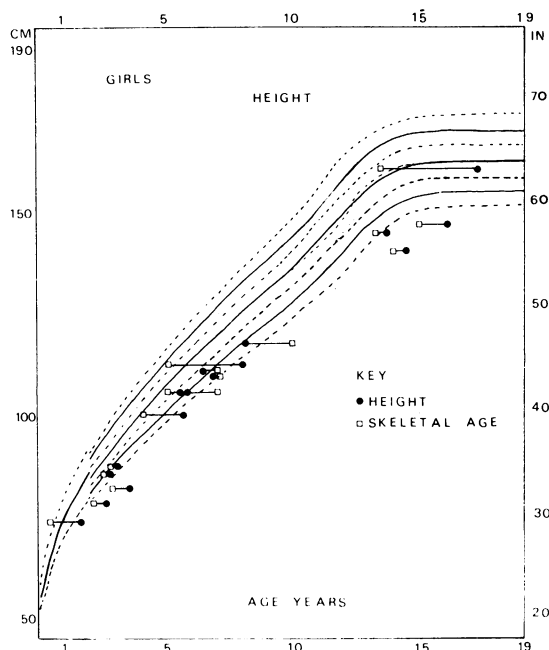


FIG. 1.—Height and skeletal age at the time of survey; 16 girls.

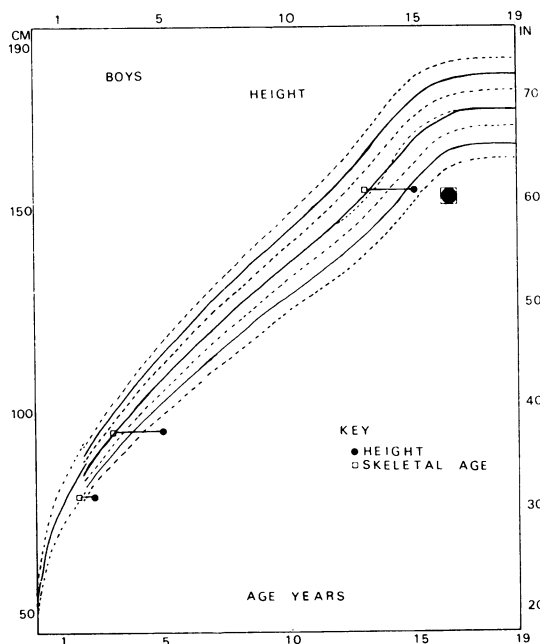


FIG. 2.—Height and skeletal age at the time of survey; 4 boys.

had additional deoxycorticosterone acetate. Of 6 children who did not receive PTMA, 5 were treated with oral cortisone and 1 with oral prednisone.

PTMA has a close therapeutic equivalence to prednisone, that is 1 mg PTMA is equivalent to 1 mg prednisone or 5 mg hydrocortisone. Using this figure it was therefore possible to calculate from the total dose of PTMA given to each child in the first year of life and from his body surface area at 6 months of age the equivalent amount of hydrocortisone/m<sup>2</sup> per day which each child received.

Data were available in 12 out of the 14 children who received PTMA to enable the height velocity in the first year of life to be plotted against this equivalent dose of hydrocortisone. Fig. 3 illustrates

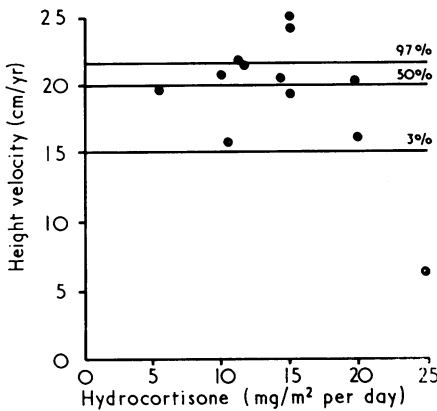


FIG. 3.—Height velocity in the first year of life plotted against steroid dosage in 12 children.

these data. The majority of the children received the equivalent of between 10 and 20 mg hydrocortisone/m<sup>2</sup> per day. The height velocities are clustered around the 50th centile. It is of significance that the one child who is below the 3rd centile received the highest dose of PTMA in the group. There are 2 children above the 97th centile and this probably indicates that they were undertreated during this period. The 6 children who were treated with oral short-acting steroid preparations are stunted in height and have retarded skeletal ages: 4 of these children lie below the 3rd centile for height, 1 lies on the 10th, and 1 on the 25th. If the steroid which they received is expressed in terms of its hydrocortisone equivalent per m<sup>2</sup> per day in the same way as the first group, it is apparent that these children received considerably more steroid than the children given long-acting steroid. The girl who is now on the 25th centile received approximately 70 mg hydrocortisone/m<sup>2</sup>

per day, as did the girl on the 10th centile. 2 of the 4 children below the 3rd centile also received this order of dosage, and a third received approximately 40 mg. The fourth, a boy, was an extremely ill child who spent his first 8 months of life in hospital and had several severe crises. The total dose of hydrocortisone and mineralocorticoid which he received was massive but it was not possible from the data available to calculate this accurately.

There were 4 girls in the group over 14 years of age. The oldest girl has a much delayed skeletal age. This may in part be related to a delayed onset of puberty. She did not start to develop secondary sexual characteristics until she was 15 years old and did not start to menstruate until January 1973 at the age of 17 years 4 months. The next 2 girls are sisters. Both are postpubertal with well-developed secondary sexual characteristics and regular menstruation. Both girls have delayed skeletal development with open epiphyses. On plotting their growth velocity curves it is apparent that they passed their pubertal growth spurt between the ages of 10 and 13 years, after which their rate of growth has steadily declined until in the last year neither girl has grown at all. The youngest of the 4 girls was 13 years 8 months at the time of the survey. She was developing signs of puberty and has recently started to menstruate. Her growth velocity curve shows that she is beginning her pubertal growth spurt.

There are 2 boys who are over 14 years of age. The older boy is postpubertal with a bone age commensurate with his chronological age. His pubertal growth spurt occurred between 13 and 15 years of age. The younger boy has well-developed secondary sexual characteristics but has not shown any evidence of a growth spurt. His bone age is retarded with open epiphyses.

In this group of 6 older children, therefore, 4 are below the 3rd centile for height, 1 is on the 10th centile and 1 on the 25th centile. All but one have retarded bone ages. This is the situation that one expects to see in steroid overdosage.

Fig. 4 illustrates the current steroid dosage for this group of children as hydrocortisone equivalent per m<sup>2</sup> per day against the height centile. Most of the children are receiving the equivalent of between 10 and 30 mg hydrocortisone/m<sup>2</sup> per day. There is a possible correlation between current dosage and current size, in that 14 out of the 20 children lie below a line drawn at 45° through the group.

### Discussion

This group of children, who are in good health, show evidence of subnormal linear growth and

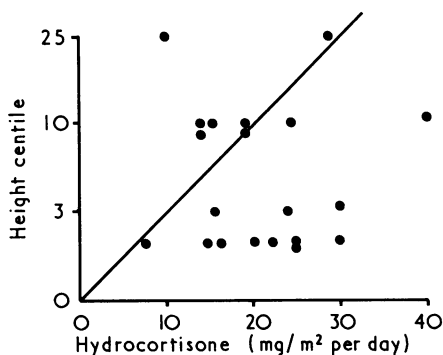


FIG. 4.—Current height achievement plotted against current steroid dosage in 20 children.

delayed skeletal maturation, which could be due to the effect of the steroid which they have received.

The dose of steroid they received when expressed in terms of its equivalent dose of hydrocortisone was well within the limits prescribed by Migeon (1968) and below those of Sperling *et al.* (1971) and Rappaport *et al.* (1968), both in the first year of life and subsequently. However, Blodgett *et al.* (1956) reported that doses of hydrocortisone between 14 and 20 mg/m<sup>2</sup> per day could produce marked growth inhibition and delayed skeletal maturation, and our dosage was certainly within or above such levels.

These children received a long-acting prednisone analogue in the first year of life and there is some evidence to suggest that such compounds cause more growth retardation than hydrocortisone. In the doses we have used there does not appear to have been any reduction of growth velocity in the first year of life in this group of children. The one child who did not achieve a normal velocity was given higher dosage and this suggests that, like most of the steroid drugs, the stunting effect of PTMA is dose related. This child's present height is on the 3rd centile. This regimen therefore provided an easily regulated reliable method of treating the children and does not appear to cause significant stunting.

If this is the case, then subsequent therapy with prednisone appears to have been the prime factor in stunting these children. Prednisone is reported to have a greater stunting effect than hydrocortisone (Van Metre, Niermann, and Rosen, 1960). Van Metre reported that doses of prednisone up to 6 mg/m<sup>2</sup> per day did not have any growth inhibiting effect. All except 3 of our group of children received less than this dose and none received more than 8 mg/m<sup>2</sup> per day.

A further possibility is that the children have been

overtreated because our criteria for control have been too strict, the acceptable levels of urinary 17-ketosteroid which we have used being slightly lower than those mentioned by Raiti and Newns (1970).

The children with retarded skeletal ages have open epiphyses, and hopefully some catch-up growth will occur with better ultimate height achievement than one would forecast at present.

In conclusion, therefore, we can say that PTMA in the first year of life provides a convenient method of control for children with this condition and in our experience does not influence rate of growth in the first year. Subsequent therapy with prednisone appears to have stunted growth in our group, due either to an effect of the drug itself or to too strict control leading to unnecessarily high dosage. For the future we are considering the use of hydrocortisone to control these children and we may relax our criteria for control while placing greater emphasis on maintaining the rate of skeletal maturation parallel to chronological age.

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