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Variations in Duration of Pubertal Growth: a Mechanism Compensating for Differences in Timing of Puberty and Minimizing their Effects on Final Height

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ABSTRACT. Bourguignon, J.P. in collaboration with the Belgian Study Group for Paediatric Endocrinology (Department of Paediatrics, University Hospital, Sart Tilman, Liège, Belgium). Variations in duration of pubertal growth: a mechanism compensating for differences in timing of puberty and minimizing their effects on final height. Acta Paediatr Scand [Suppl] 347:16, 1988.

It is unclear how important age at onset of puberty is for adult stature. The growth effects of differences in timing of puberty have been studied on a bone age basis in 22 hypopituitary boys and on a chronological age basis in male subjects with early, normal or delayed onset of puberty. Very early onset of puberty results in short adult stature. This is because a marked reduction of prepubertal height gain is only partially compensated for by an increase in pubertal height gain. In contrast, very late onset of puberty determines no increase or a minor increase in adult stature. This results from a reduction in pubertal height gain, counterbalancing the increased prepubertal height gain. Differences in duration of growth are the major factor accounting for the different height gains observed in relation to timing of puberty, while mean growth rate shows only minor changes. The differences in duration of pubertal growth are paralleled by differences in the rate of bone maturation, which therefore do not account for differences in duration of puberty. It is concluded that, except in severely precocious puberty, manipulation of the timing of puberty is unlikely to affect final height to any great extent. *Key words: Growth, puberty, final height, hypopituitarism.*

Important questions may be addressed in relation to the possible effects of differences in age at onset of puberty on final stature.

- In patients with precocious puberty, what are the upper age limits for beginning and stopping gonadotrophin releasing hormone (GnRH) agonist therapy?
- In patients with isolated growth hormone (GH) deficiency or very short stature of familial, genetic or unknown origin, what is the rationale for delaying puberty using GnRH agonists?
- In patients with panhypopituitarism or gonadal dysgenesis, what is the optimal age for induction of pubertal development?

Definitive answers to these specific questions must await the results of many years of study before final height is attained.

This paper examines the role of the timing of puberty in adult stature on two different age bases. Bone age was used as a basis in 22 GH treated hypopituitary boys beginning puberty between 11.2 and 15.4 years of bone age (1), whereas chronological age was used to compare boys with very early puberty (2,3), physiological variants of normal pubertal timing (4) or pituitary hormone deficiencies resulting in severely delayed puberty (1,5,6). While very few data have been published on the final growth status in boys with untreated idiopathic precocious puberty, the observations of very late puberty have most commonly been obtained in male patients with idiopathic hypopituitarism or hypogonadotrophic hypogonadism. For this reason only male subjects or patients are examined in this study. In addition, patients with organic aetiologies were excluded in order to avoid any possible interaction of the underlying disease or therapy with growth.

PATIENTS AND METHODS

A total of 22 hypopituitary boys were studied. Spontaneous puberty developed in 8 patients, and 14 were treated with testosterone enanthate, 100 mg/month i.m. These patients will be referred to in the figures as groups A and B, respectively. Treatment with pituitary GH (Crescormon[1]), 6 IU 3 times/week, was given intramuscularly throughout the entire study, the dose being increased up to 8 IU 3 times/week during spontaneous puberty. When required, appropriate replacement therapy with cortisone, thyroxine and vasopressin were also given and regularly adjusted. Detailed data on these patients have been published in a collaborative study from the Belgian Study Group for Paediatric Endocrinology (1).

Growth data compiled from the literature are included in this study. From the observations of Thamdrup (2) and Sigurjonsdottir and Hayles (3), data were obtained on 5 and 4 boys, respectively, with idiopathic precocious puberty beginning respectively before 2 years of chronological age and at a mean age of 3.9 years. These patients will be referred to as groups C and D, respectively. Growth data on 9 boys (7–10) with untreated congenital adrenal hyperplasia (classical form) were also used (Group E). The longitudinal observations of Tanner and Davies (4) in boys maturing at early, average and late tempos (groups F,G,H) were used as well. Finally, observations obtained in patients with Kallman's syndrome are included (5,6), referred to as group J.

Two periods of growth were studied. Prepubertal growth was arbitrarily considered to extend from the age of 2 years to the age when the first signs of testicular development (testicular volume $\geq$ 4ml) were seen or, in patients with gonadotrophin deficiency, when testosterone treatment was started. The period of pubertal growth was considered to end when height velocity had dropped below 2cm/year. These age limits were chosen in order to obtain a mean growth rate not influenced by the periods of very fast or very slow growth seen during infancy and after puberty.

In order to evaluate prepubertal and pubertal growth, total height gain was calculated during both periods. From the total height gain and the duration of each period, the mean growth rate was calculated based on the equation:

$$\text{height gain} = \text{height velocity} \times \text{duration}$$

During puberty, peak height velocity was studied. In patients with hypopituitarism or precocious puberty, no smoothing analysis of growth data was performed. Peak height velocity was calculated as the maximal growth rate seen over 1 year using growth data obtained every 3 months. In hypopituitary patients, bone age was estimated every year according to Tanner *et al.* (11).

RESULTS AND DISCUSSION

Index of pubertal growth spurt. Traditionally, peak height velocity is used to evaluate the pubertal growth spurt. For many years, it has been known that the amplitude of the peak height velocity decreases with age at the onset of puberty (12–14). As long as the breadth of the growth spurt shows small age-related variations which parallel the differences in amplitude, peak height velocity is an appropriate index of pubertal growth. Such an observation is made when comparing normal children growing at different tempos (13).

In very late puberty, important changes in the breadth of the growth spurt may occur, as shown in Fig. 1. In 22 hypopituitary boys, both peak height velocity and total pubertal height gain were negatively related to bone age at onset of puberty. However, according to the slopes of these correlations, a 22% reduction of peak height velocity occurs between 11.0 and 15.0 years of bone age, while total pubertal height gain shows a 57% decrease at the same time. This suggests the important role of a reduced duration of pubertal growth which will affect total pubertal height gain to a greater extent than peak height velocity. Therefore, the former index should be preferred to the latter for evaluating growth in very late puberty.

Pubertal height gain in relation to timing of puberty. Fig. 2 shows the differences in pubertal growth in relation to age at onset of puberty in hypopituitary boys entering puberty between 11.2 and 15.4 years of bone age, and in several groups of subjects or patients starting puberty between 2 years and 18.5 years of chronological age. Total pubertal height gain is negatively related to age at the onset of puberty (Fig. 2a). The decrease in pubertal height gain is dependent on a reduction in the duration of pubertal growth (Fig. 2b), while mean pubertal growth rate is not significantly related to age at the onset of puberty (Fig. 2c).

[1] Crescormon, trademark KabiVitrum AB, Sweden, for pituitary GH, withdrawn worldwide April 1985

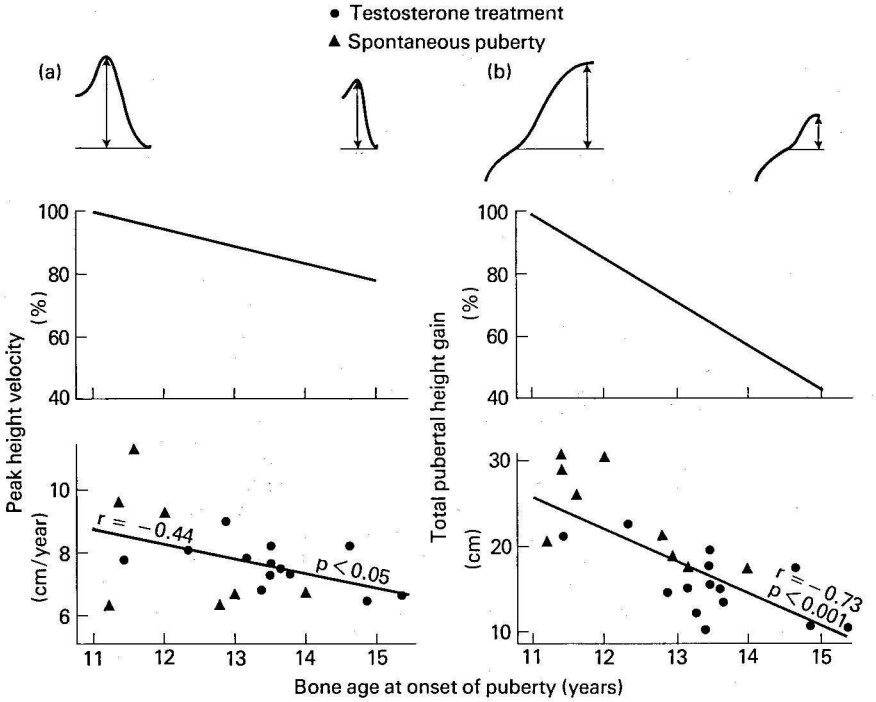

Fig. 1. (a) Peak height velocity and (b) total pubertal height gain in relation to bone age at the onset of puberty in 22 hypopituitary boys during spontaneous or testosterone induced puberty. Individual data are shown in the lower graphs. The upper graphs represent the slopes of the correlations as a percentage of the values seen at 11.0 years of bone age. Differences in peak height velocity and total pubertal height gain are schematically illustrated by the arrows.

A similar role for the duration of puberty is obvious when evaluation of pubertal growth is based on chronological age.

Bone maturation rate in relation to timing of puberty. The rate of bone maturation has been studied, as a rapid rate of bone maturation may determine a reduced duration of growth, while a slow progression of bone age may result in a prolonged duration of growth. In hypopituitary boys, the rate of bone maturation (△ bone age/△ chronological age) during puberty is inversely related to bone age at the onset of puberty (Fig. 3). Consequently, differences in the rate of bone maturation do not account for differences in the duration of puberty. Rather, the rapid rate of skeletal maturation occurring at early bone ages may be opposed by the compensatory increase in duration of pubertal growth seen in patients with early puberty. Conversely, the slow rate of skeletal maturation seen at late bone ages may be opposed by the compensatory reduction in duration of pubertal growth seen in patients with very late puberty.

Implications of variations in duration of pubertal growth. As shown in Fig. 1, the differences in duration of pubertal growth related to age at the onset of puberty will affect the breadth of the growth spurt. Consequently, total pubertal height gain seems to be a more appropriate index than peak height velocity in patients with abnormal timing of onset of puberty. In addition, studies performed before adult height is attained are biased by the differences in duration of puberty. As shown in Fig. 4, the height gained after 2 years of puberty in hypopituitary patients is not significantly related to bone age at the onset of puberty. However, a significant relationship is found when total pubertal height gain is studied, because of the longer duration of puberty in patients starting puberty at early bone

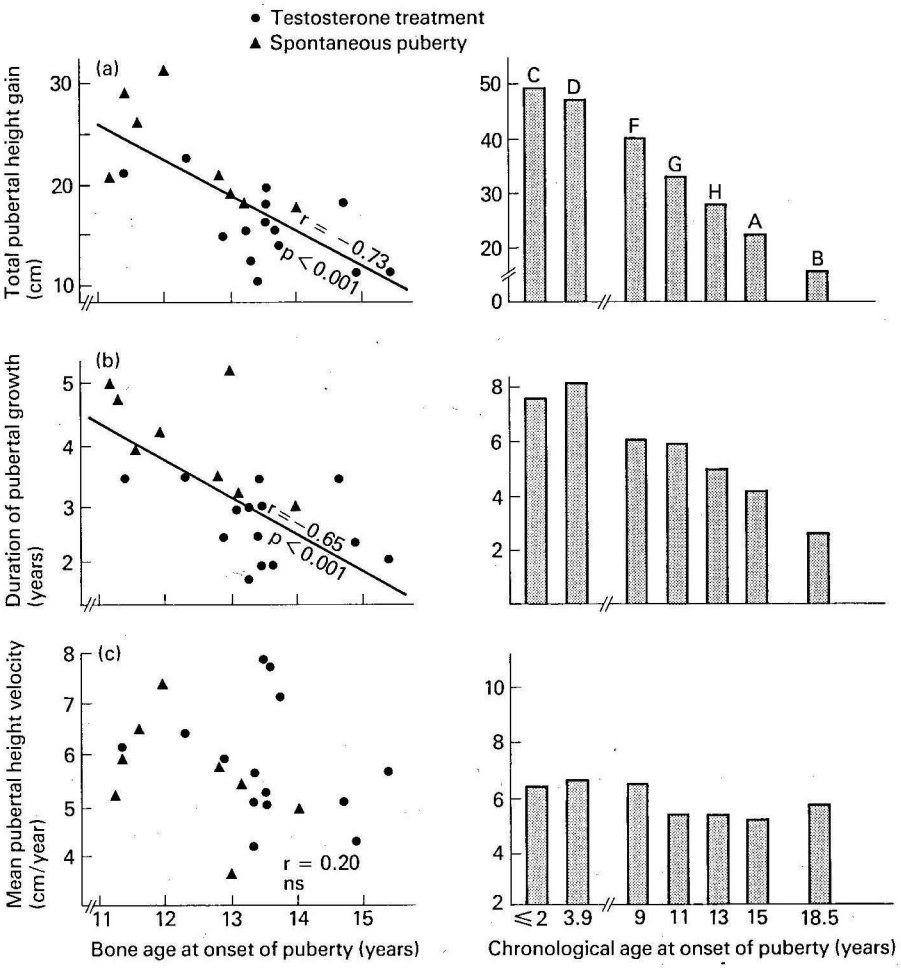

Fig. 2. (a) Total pubertal height gain (b) duration of pubertal growth and (c) mean pubertal growth rate in relation to age at onset of puberty. Individual data of hypopituitary boys are shown in relation to bone age (left). Data obtained in several groups of male subjects or patients (see METHODS section for definition) are shown in relation to chronological age (right).

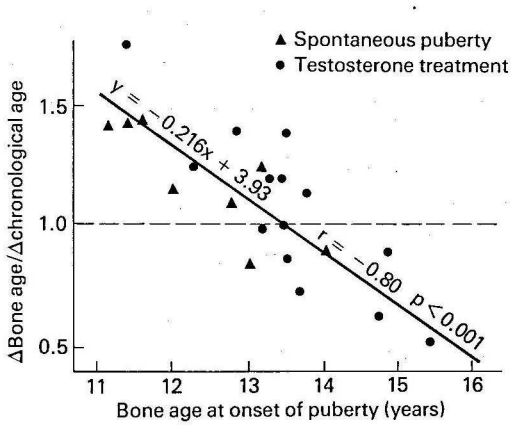

Fig. 3. Rate of bone maturation in relation to bone age at onset of puberty in hypopituitary boys.

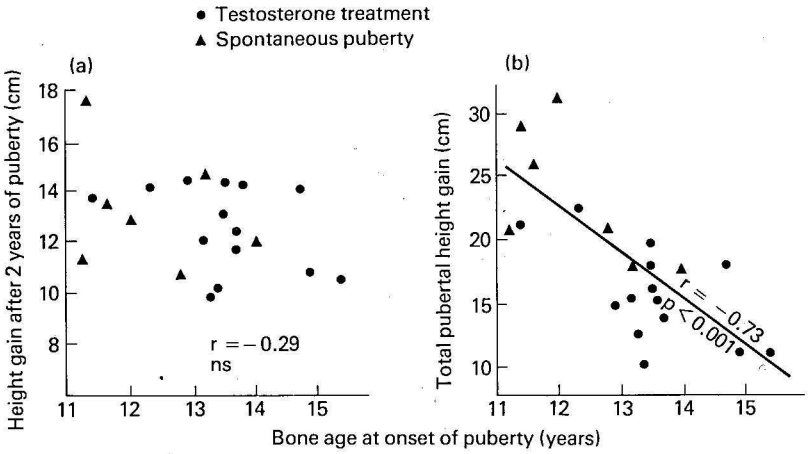

Fig. 4. Pubertal height gain of hypopituitary patients evaluated (a) after 2 years of pubertal growth or (b) after completion of pubertal growth, in relation to bone age at the onset of puberty.

ages. Thus, studies on the early growth response to sex steroids at puberty may not help in elucidating the importance of pubertal height gain and predicting its contribution to adult stature.

Prepubertal height gain in relation to timing of puberty. Fig. 5 shows differences in prepubertal growth in relation to age at the onset of puberty. By definition, differences in age at the onset of puberty account for the variability in the duration of prepubertal growth (Fig. 5b), and also the variability in prepubertal height gain (Fig. 5a). This effect is modulated by the age-related decrease in mean growth rate (Fig. 5c). Children with very early puberty have lost several years of prepubertal growth which would have occurred at a quite rapid rate of, for example, more than 6 cm/year; therefore, they have a substantial reduction of prepubertal height gain. In contrast, children with very late puberty experience several extra years of prepubertal growth which occurs at a slower rate closer to 4 cm/year. Therefore, they have a slightly increased prepubertal height gain.

In hypopituitary boys, the slow growth rate seen before puberty is not significantly related to bone age when considering only data obtained after the first year of GH therapy in order to exclude the initial catch-up of growth (Fig. 5). This also indicates that differences in prepubertal growth rate play a more important role in very early puberty than in very late puberty.

Final height in relation to timing of puberty. As shown in Fig. 6, boys with untreated congenital adrenal hyperplasia (group E) or with idiopathic precocious puberty (groups C and D) have a reduced final height. This is because prepubertal growth is severely reduced and incompletely compensated for by an increased pubertal height gain. When studying boys maturing at early, normal or slow tempos (groups F, G, H) and patients with Kallman's syndrome (group J), no difference or only a minimal increase in final height is observed. In fact, the differences in prepubertal growth, as indicated by height at the onset of puberty, are counterbalanced by opposite variations in pubertal height gain. A similar observation is made when comparing hypopituitary boys with spontaneous puberty (group A) to those treated using testosterone (group B). Analysis of individual growth data obtained in these patients in relation to bone age confirms the existence of opposite variations in prepubertal and pubertal growth which account for the absence of obvious differences in final height (Fig. 6).

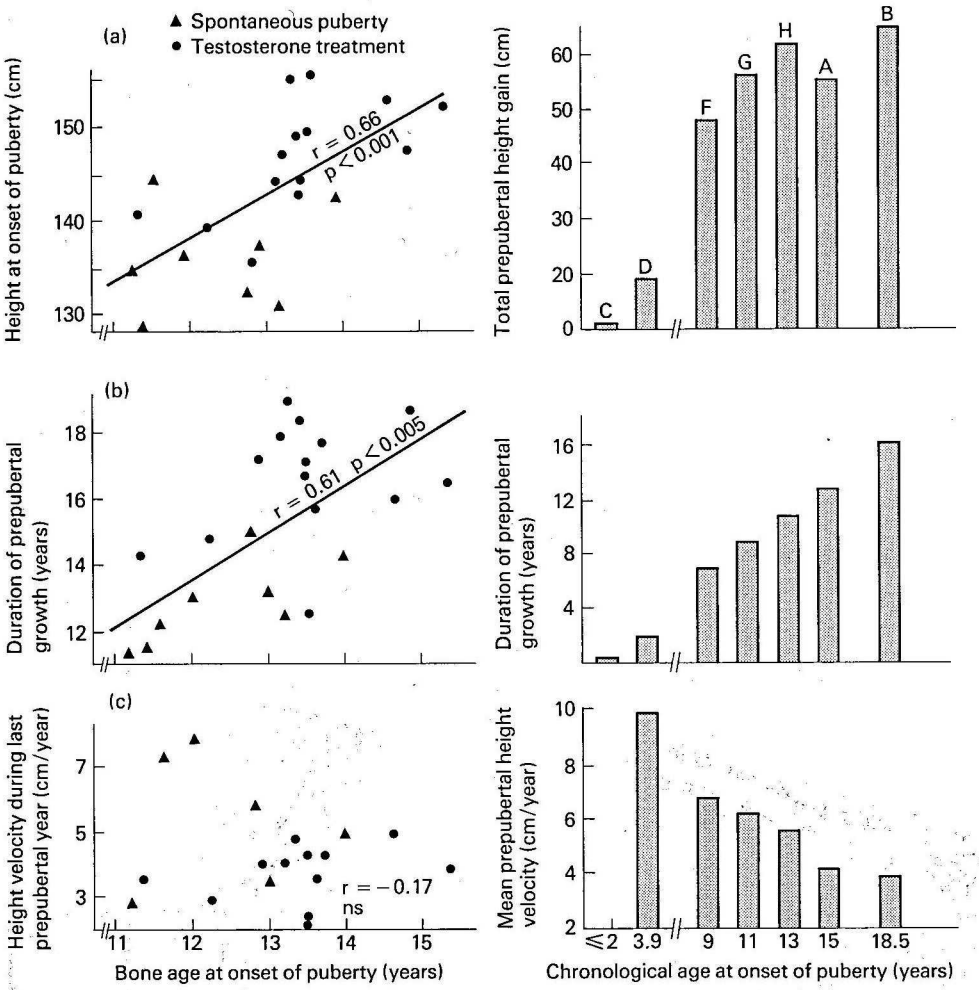

Fig. 5. (a) Total prepubertal height gain (b) duration of prepubertal growth and (c) mean prepubertal growth rate in relation to age at onset of puberty. Individual data of hypopituitary boys are also shown in relation to bone age. Data obtained in several groups of male subjects or patients (see METHODS section for definition) are shown in relation to chronological age.

COMMENTS

From the evaluation of auxological findings, it is possible to understand how advancement of the timing of puberty will reduce final height, while delay of puberty will not significantly affect final height. Differences in the duration of puberty play a major role in explaining these observations. Previous authors, particularly Prader (15,16), have emphasized the concept that manipulation of the timing of puberty would not result in significant differences in final height. This paper provides some insight into the mechanisms explaining this relatively minor role of timing of puberty. According to the data presented, a late start of sex steroid therapy in hypogonadal patients can no longer be recommended in order to improve final height. In addition, it does not seem reasonable to propose therapies delaying puberty in an attempt to increase final height in short subjects who are 'on time' for sexual development. However, careful studies conducted until adult height is attained are required before any conclusions can be drawn in specific situations.

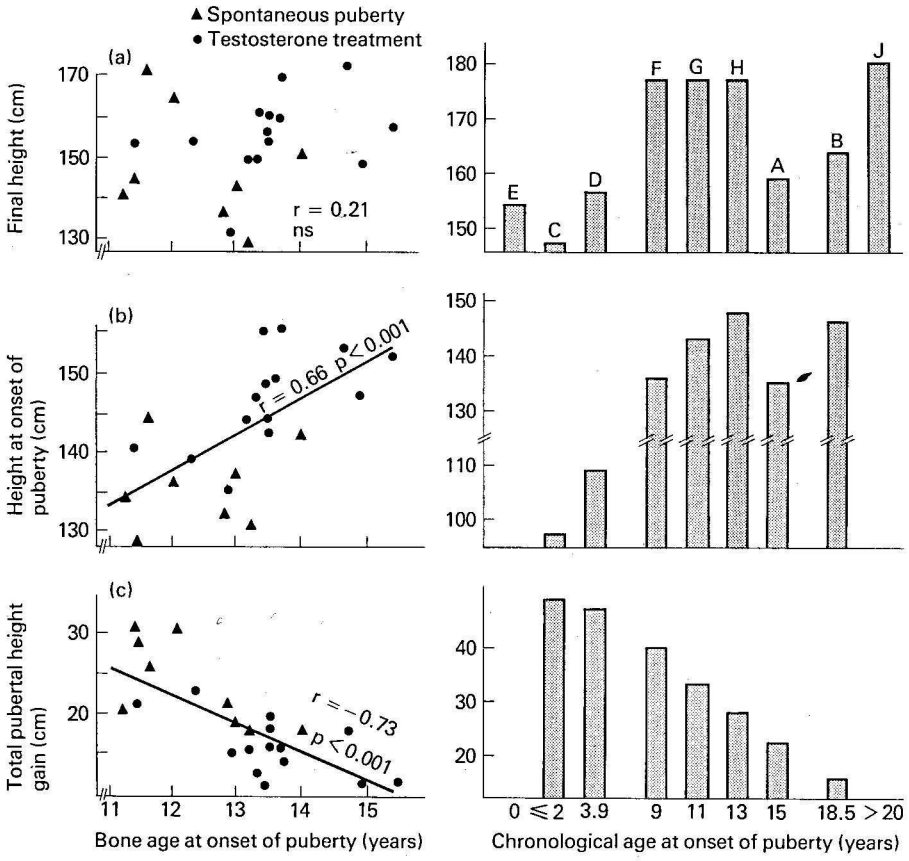

Fig. 6. (a) Final height (b) height at onset of puberty and (c) total pubertal height gain in relation to age at the onset of puberty. Individual data of hypopituitary boys are shown in relation to bone age (left). Data obtained in several groups of male subjects or patients (see METHODS section for definition) are shown in relation to chronological age (right).

in an attempt to increase final height in short subjects who are 'on time' for sexual development. However, careful studies conducted until adult height is attained are required before any conclusions can be drawn in specific situations.

The observations made in male subjects are not relevant to female pubertal growth, which follows a different time sequence. The few data available in female patients suggests that age, particularly bone age, may be critical for the growth response to sex steroids (17). This warrants further study, bearing in mind that conclusions drawn from an early response to therapy may not necessarily apply to final height.

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DISCUSSION

J Sack (Israel): Do you consider that it would be wrong to treat children who have a normal onset of puberty to delay their puberty in order to achieve greater final height? Some people deduce from the situation with precocious puberty that it might be good to treat short normal children with normal puberty with a GnRH analogue (LHRH) in order to delay their puberty and achieve a higher final height. What would you think about this?

JP Bourguignon: I think that we could not state that such a proposal is wrong until we have the results of well conducted research – I think a double-blind placebo-controlled study on this subject is in progress in NIH. But the data available so far do not support suggestions that there would be any consistent benefit in terms of final height in delaying puberty.

MB Ranke (Tübingen, West Germany): In your view, what is the critical age at which an

early start of puberty reduces final height in girls and boys?

JP Bourguignon: I am not sure I can answer this question. The answer might come from studies in patients with untreated precocious puberty, and as you know there are very few data available on this topic. We do have evidence that boys starting puberty by the age of 9 years have a similar final height to patients starting puberty later.

NE Skakkebaek (Copenhagen, Denmark): I think one other dimension should be recalled when we talk about growth in children with delayed puberty, which is that delayed puberty might cause disproportionate growth. Using drugs to extend the prepubertal period might also have a similar influence which should be taken into consideration.

JP Bourguignon: I think that is an appropriate comment, but we have no data on this particular point.

P Sizonenko (Geneva, Switzerland): I would like you to elaborate on partial compensation, that is, if more prepubertal growth occurs, which could be compensated by a smaller height gain during puberty. My feeling in looking at your scheme is that we cannot change final height at all. For example, if we treat with sex steroids a patient who is insufficient in growth hormone (GH), how can we influence final height by our treatment?

JP Bourguignon: Part of the answer may be provided by studies indicating that in hypopituitary patients final height correlates best with height at onset of puberty. This indicates that the prepubertal period is the most critical one in terms of modulating final height. This is not really contradictory with the evidence presented, because most of the data on the effects of treatment on final height have focused on pubertal growth, particularly as far as GH dosage is concerned, as these patients have a reduced height velocity before onset of puberty. We might consider giving an increased dosage of GH before puberty, rather than during puberty.