SHORT TERM GROWTH IN TALL AND SHORT STATURED ADOLESCENTS TREATED WITH SEX HORMONES

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1. VALK I M and van den BOSCH J S G (1978): Intradaily variation of the human ulnar length and short term growth - A longitudinal study in eleven boys. Growth 42: 107.

2. van den BOSCH J S G, SMALS A G H, KLOPPENBORG P W C and VALK I M (1979): Short term growth in boys with delayed puberty after diagnostic human chorionic gonadotropin administration. J Clin Endocrinol Metab 49: 387.

3. van den BOSCH J S G, SMALS A G H, VALK I M and KLOPPENBORG P W C: Lack of difference in growth stimulating effect between weekly single and multiple human chorionic gonadotropin administration in boys with delayed puberty. Clinical Endocrinology, in press.

4. van den BOSCH J S G, SMALS A G H, KLOPPENBORG P W C and VALK I M (1981): The effect of low dose estrogens on short term growth and concomitant biochemical phenomena in girls with tall stature. Acta Endocrinol (Kbh) 98: 156.

5. van den BOSCH J S G, SMALS A G H, PIETERS G F F M, VALK I M and KLOPPENBORG P W C: Instant growth inhibition by low dose estrogens in excessively tall boys. Acta Endocrinol (Kbh), in press.

CONTENTS

"Misce stultitiam consiliis brevem"

"Meng onder uw ernstige bezigheden

een weinig dwaasheid"

(Horatius, Carmina)

CHAPTER 1

INTRODUCTION

INTRODUCTION

Short term growth studies as are reported in this thesis have become possible with the development of the ulnar length measuring technique by Valk (1-2). The technical performance of the device as well as the methodological approach of growth enable reliable detection of growth in ulnar length within time periods covering one third of the time needed with conventional body height measurements (3). The choice of the ulna as object of this measuring technique was based on several grounds: one being the high correlation found earlier between body growth and growth in the length of the forearm (4-5), another the fact that herewith endochondral growth of one long bone could be studied. The third reason was a practical one since adequate positioning of the forearm is relatively easy to perform and convenient to both patient and observer.

As to the technical aspects there are two important issues to be mentioned here. First the fact that this technique is not invasive which makes it applicable as frequently as wanted, even several times a day as is illustrated in chapter one. This in contrast to earlier reported conventional X-ray studies (6-9) and the recently developed Roentgen stereophotogrammetric method (8) which was used by Aronson for growth studies (9). This latter technique is even more invasive since it necessitates the implant of metalic markers and the use of X-rays for each length determination. The second important issue of the ulnar length measuring technique is the attainment of maximal reproducibility of the position of the forearm by a fixing apparatus (1). Lack of reproducibility of the position chosen is one of the very errors in body height measurements. Reproducibility in this determi-

nation can only be achieved by quickly repeated body height measurements since, as Lewin demonstrated (10-11), the extent of the measurement error is time dependent: the longer the time interval between the measurements the higher the error. This time dependent effect on the error of measurement is eliminated in the ulnar length measuring technique since the fixing apparatus ensures a precisely reproducible position of the forearm over short as well long time periods.

The most important methodological issue is the choice of determining the change in ulnar length i.e. the growth rate rather than the absolute ulnar length, since only this provides a direct insight in actual growth activity. This is expressed by using the Three week Ulnar Growth rate i.e. TUG-rate (mm) as outcome of the determination. Especially in response studies as described in the following chapters the increment method is to prefer above absolute lengths, because the effect of the therapy on growth velocity is directly illustrated. But also longer term evaluation of intra- and interindividual growth activity in the adolescent growth spurt is reflected better by the growth rate since Tanner stated: "....the amount of height added during the spurt is to a considerable degree independent of the amount attained before" (12). This was confirmed for growth in ulnar length. The correlation between ulnar length attained before puberty and length added during the spurt was very poor, ranging from $r = 0.06$ to $r = 0.11$ (13).

Another essential methodological aspect is that each determination comprises six successive independent measurements. This provides a mode to calculate a limit of confidence enabling instant statistical testing of each separate TUG-rate, which is essential for evaluation of short term growth in individual subjects. The mean stan-

dard error (SE) of the samples in the studies reported here amounts to 0.09 mm from which a mean limit of confidence of 0.18 mm (1.96 x SE) can be derived.

The study on ulnar growth in boys around the age of puberty (3) resulted in mean values for normal prepubertal and pubertal ulnar growth rates, being 0.60 and 1.00 mm per three weeks respectively. Furthermore it was demonstrated that growth in body height is approximately five times higher than growth in ulnar length, the correlation between the two being as high as 0.83. Unpublished data on normal girls reveal virtually the same mean prepubertal and pubertal TUG-rates as in boys. These growth rates are used as reference for evaluation of growth rates in children with growth disorders.

Before introducing the following chapters separately a few general remarks on the patients studied have to be made. All patients were screened thoroughly in order to exclude endocrine disorders. So patients participating in these studies in fact show a variant of normal growth (14-16). They can be grossly divided into two groups: those who are 2 standard deviations (SD) or more below and those who are 2 SD or more above the 50th centile for body height in normal Dutch children (17). The patients below the 10th centile were all boys with constitutional delay in growth and sexual development. The patients above the 97th centile were both girls and boys with tall stature. Treatment was only started in the subjects with serious psychological problems because of their outstanding position amongst their peers. The number of adolescents seeking help for these problems due to either short or tall stature is estimated to be about 25‰ (18-19), which is much higher than the number of adolescent patients with endocrine disorders as the cause of excessively tall or short stature.

However, before patients treated for growth disorders could be studied one problem had to be solved, i.e. the phenomenon of transitional changes in ulnar length during the day (3). This was important since the extent of these transitional changes might influence evaluation of growth rates on the very short term. In the second chapter the results are described of a study on the intradaily variation of the ulnar length in eleven normal boys. Since the study period covered a time interval of three weeks, growth in ulnar length was also studied. The outcome of this study appeared to be of utmost importance in evaluating the effects of drug administration in subjects with growth disorders.

The next chapter reports on the growth promoting effect of diagnostic use of human chorionic gonadotropin (hGC) in a group of boys with delay in growth and sexual development. The dose hCG given was 1 x 1500 IU on three consecutive days for assessment of the androgenic responsiveness of the Leydig cell. The growth promoting effect of hCG is known since 1940 (20), but was never studied before on this short term after such low dose.

Chapter four compares two therapeutic hCG regimens in two groups of boys with delayed puberty. In view of the reported temporal irresponsiveness of the Leydig cell to successive hCG injections (21-23) and the results described in chapter two it was thought worthwhile to compare the responses in growth rates after a weekly single dose of hCG (1 x 1500 IU) and the usually recommended weekly multiple hCG regimen (3 x 1500 IU) (24-26).

The following two chapters deal with estrogen therapy in tall girls and tall boys. Rather high dose estrogen therapy in tall girls is in focus and ample reports have appeared in literature. In chapter five the effect of

low dose of estrogen on growth in tall girls is studied. The aim of the study was to demonstrate that even a low dose of estrogens decelerates growth velocity and does so instantly.

Chapter six for the first time reports on the results of a similar low dose estrogen administration in tall boys. Especially in these boys instant growth inhibition is often of great importance. The usually recommended androgen therapy, however, exerts growth promotion in the initial phase of therapy (27-28). The study was started in view of recent data on the mode of action by which estrogens effectuate an instant growth inhibition by lowering plasma somatomedin levels (19,29).

Except for the effect on growth velocity per se, concomitant changes in growth related biochemical parameters were also studied in order to correlate them with the changes in TUG-rates.

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CHAPTER 2

INTRADAILY VARIATION OF THE HUMAN ULNAR LENGTH AND SHORT TERM GROWTH - A LONGITUDINAL STUDY IN ELEVEN BOYS

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J.S.G. VAN DEN BOSCH

SUMMARY

In order to detect the intradaily variation of the clinical ulnar length in eleven boys the right ulnar length was determined using a condylograph at seven set times of each day during a study period of three weeks.

The mean standard error of the determinations amounted 0.09 mm. In 86% of the days concerned the ulnar length changed significantly (one way analysis of variance, $p < 0.05$). As far as the whole group was concerned the ulnar length decreased significantly during the time interval from 8.00 h to 12.00 h (Friedman's related samples test, $p < 0.01$). The decrement amounted 0.4 mm. During the rest of the day the changes in the ulnar length were not significant. A consistent decrement of the ulnar length during the day in combination with total growth of 0.99 mm during the three week study period suggested that growth in length of the human ulna occurs during the night.

INTRODUCTION

The human ulnar length can be determined relatively accurately using a condylograph (1-2). The major problem in this determination is the dynamics of the soft tissues inclusive of the epiphyseal discs (3). The transient changes in the ulnar length as mentioned in an earlier publication (4) are the consequences of the dynamics of the soft tissues. Unpublished results of measurements of the ulnar length in the same individuals at different moments of the day suggested that the transient changes in the ulnar length might follow a pattern during the day. It was thought worthwhile to investigate the intradaily variation in the ulnar length.

In our laboratory short term ulnar growth is mostly investigated over time intervals of three weeks (1-2,4). Therefore we were interested in the intradaily variation of the ulnar length over that period. This time interval enabled the investigation of the total growth in length of the ulna during the whole study period.

MATERIALS AND METHODS

Eleven boys of a boarding school participated in this study. In order to follow the changes in the ulnar length during the day, their right ulnar length was determined as often as possible at seven chosen set times, during a study period of three weeks, at all days of the week except for the weekends. The mean age of the group studied was 11.54 years (ranging from 9.5 to 12.5 years). The ulnar length was measured using the ulnar measuring technique described earlier (1-2). Each determination comprised six successive independent measurements. All the

measurements were performed by one and the same observer.

The standard deviation of the error of measurement was 0.22 mm. A mean standard error of the samples amounting 0.09 mm can be derived.

The occurrence of significant changes in ulnar length during the day was tested for each subject, and each day separately using the one way analysis of variance.

Whether differences between the ulnar length at the seven time moments of the day were significant for the whole group was tested using Friedman's related samples test. In order to detect the time intervals during which the ulnar length changed significantly, the signed rank test for paired observations was used.

The total ulnar growth during the whole study period was assessed for each single individual by subtracting the mean ulnar length of the last day of the study period from the mean ulnar length of the first day. The significance of the changes in the ulnar lengths was tested using the Student's T-test.

RESULTS

In table 1 the mean ulnar lengths at seven moments of the day are tabulated for each individual separately. It is to be remembered that these means are calculated from the results of the measurements at the corresponding time moments of all the days concerned. Due to social interference, the intended number of 176 days of investigation - 16 days of investigation on 11 boys - was not reached. The actual number of days of investigation amounted 134. In 86% (115) of the days of investigation (134) the ulnar length changed significantly within the time interval from 8.00 h to 18.00 h (one way analysis of variance, $p < 0.05$).

In figure 1 the mean ulnar lengths at seven moments of the day are illustrated for the whole group.

Table 1 and figure 1 reveal that as far as the whole group is concerned the length of the ulna is longest early in the morning and shortest at noon. For the whole group studied the means of the ulnar lengths differ significantly during the day (Friedman's related samples test, $p < 0.01$). During the time interval from 8.00 h till 12.00 h the ulnar length decreases 0.4 mm (signed rank test, $p < 0.05$). During the time interval from 12.00 h till 13.00 h the ulnar length increases 0.12 mm. From 13.00 h till 17.00 h the ulnar length increases 0.06 mm. From 17.00 h till 18.00 h there is a decrement amounting 0.06 mm. The changes after 12.00 h are not significant (signed rank test, $p > 0.05$).

In table 2 the mean ulnar length at the first day and at the last day of the study period are compiled for each

Subj. no.	Moments of the day (hr)						
	08.00	10.00	12.00	13.00	16.00	17.00	18.00
1	226.66	226.80	226.77	226.58	226.53	226.75	226.58
2	215.94	215.84	216.12	215.59	215.84	215.79	215.69
3	219.08	219.03	218.35	218.93	218.96	219.06	219.84
4	224.19	223.98	223.84	223.79	223.82	223.77	223.74
5	249.93	249.70	248.95	249.74	249.71	249.88	249.49
6	256.57	256.44	256.41	256.39	256.44	256.30	256.44
7	219.77	219.34	219.91	219.60	219.59	219.66	219.70
8	243.77	243.64	243.25	243.24	243.40	243.32	243.30
9	235.20	234.83	233.92	234.85	235.12	234.99	235.03
10	241.82	241.15	241.53	241.59	241.41	241.32	241.60
11	229.82	229.62	229.32	229.45	229.43	229.58	229.45

TABLE 1. The means of the mean ulnar lengths at seven moments of the day of a three week study period in eleven boys of a boarding-school, expressed in mm.

individual separately. The difference between the mean ulnar length of the first day and the last day of the study period appeared to be significant in all subjects concerned (Student's T-test, $p < 0.01$). From table 2, excluding the results of the subjects 7 and 10, a mean three week ulnar growth rate of 0.99 mm can be calculated.

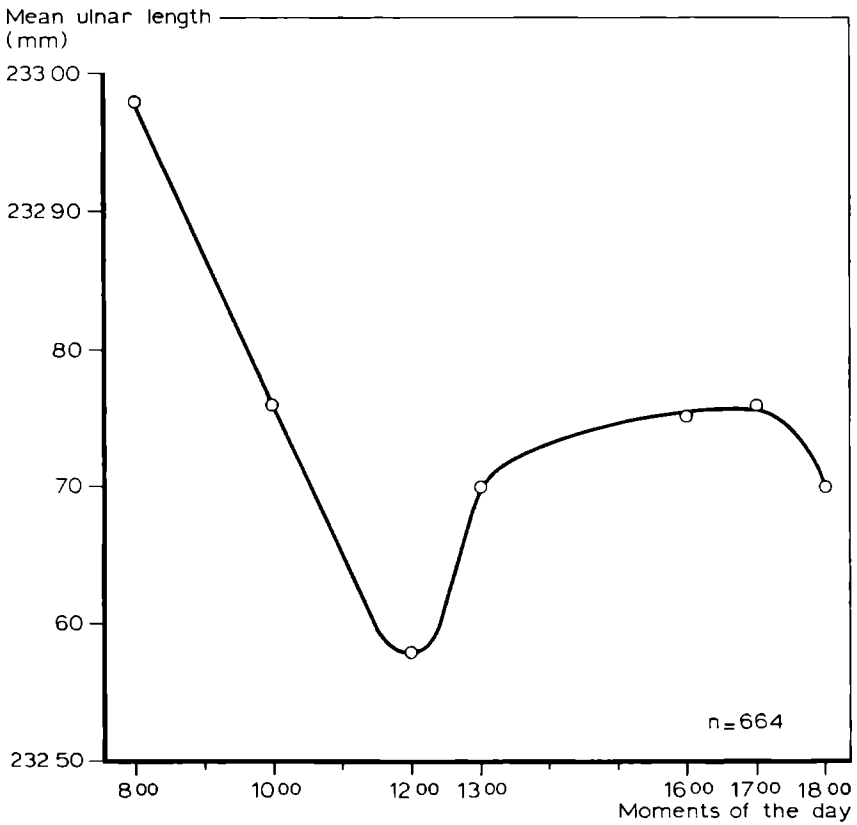

FIG. 1. The mean ulnar length at seven moments of the day in eleven boys.

Subj. no.	mean ulnar length in mm	
	date: 13 01 75	date: 03 02 75
1	225.55	226.63
2	215.13	216.37
3	218.13	219.11
4	223.40	223.92
5	218.91	220.43
6	256.08	256.76
7	219.47	219.86*
8	242.94	243.63
9	233.97	235.41
10	241.14	241.73**
11	229.12	229.66

*date: 23 01 75; **date 22 01 75

TABLE 2. The mean ulnar length of the first and the last day of a three week study period in eleven boys.

DISCUSSION

In the group of eleven boys studied the intradaily changes of the clinical ulnar length follow a pattern. The ulnar length decreases significantly during the morning, 0.4 mm during the time interval of four hours.

The occurrence of intradaily rhythms in the ulnar length must be taken into account whenever short term ulnar growth studies are made with the measuring technique used. The results of this short term longitudinal study revealed a mean total ulnar growth of 0.99 mm during the whole three week study period. This finding is in accordance with the three week ulnar growth rate in boys around the age of puberty as earlier reported (4).

The facts: i a consistent decrement of the ulnar length during the day, ii the insignificant changes from noon to 18.00 h and iii the total growth during the three week study period suggest that growth in length of the human ulna occurs during the night.

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CHAPTER 3

SHORT TERM GROWTH IN BOYS WITH DELAYED PUBERTY AFTER DIAGNOSTIC HUMAN CHORIONIC GONADOTROPIN ADMINISTRATION

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SUMMARY

Using a sensitive measuring device, three-day hCG administration (Pregnyl; 1500 IU daily) was shown to temporarily increase ulnar growth velocity from prepubertal (0.40 ± 0.35 mm/three weeks) to pubertal values (1.1 ± 0.64 mm/three weeks) in ten boys with delayed puberty.

The growth-promoting effect of diagnostic hCG administration, which was demonstrable for three to nine weeks, was associated with an overt rise in plasma testosterone from 129 ± 126 to 818 ± 419 ng/100 ml and an approximate doubling of the serum alkaline phosphatase activities from 193 ± 46 to 376 ± 115 U/liter, suggesting an initiated growth spurt.

INTRODUCTION

The Leydig cell responses to short term hCG administration are well documented in literature (1-5). Since Dorff (6) in 1940 reported on the beneficial effects of long term administration of hCG on growth and development in patients with constitutional growth retardation, ample reports have appeared in literature on the growth-promoting effect of either endogenous or exogenous testosterone administration (6-8)

To our knowledge, however, the effect of diagnostic hCG administration on short term growth has never been described. Since the development of a sensitive measuring device by Valk (9-10) enables accurate measurement of the ulnar length (9-12), it was thought worthwhile to study the effect of a three-day hCG stimulation test in boys with delayed puberty.

MATERIALS AND METHODS

Ten boys with constitutionally delayed puberty participated in this study. The mean age (± SD) was 15.1 ± 1.1 yr, whereas the skeletal age, according to Greulich and Pyle (13), was 11.4 ± 0.7 yr. Body height amounted to 150.6 ± 9.1 cm and was below the 10th percentile for Dutch children (14) in nine of the ten boys. Body weight was 42.7 ± 12.6 kg and was below the 10th percentile for seven out of 10 boys. All boys were in Tanner stage I-II.

During a clinical stay of one to two weeks for endocrinological evaluation of their growth retardation, 1500 IU hCG (Pregnyl^{R}) were given im during three consecutive days for diagnostic purposes. Blood for testosterone and alkaline phosphatase measurements was sampled before and

after hCG administration. Measurements of ulnar length and body height were performed in all boys during three consecutive periods: 1) the period preceding the hCG loading (mean duration 9.2 ± 5.0 weeks; range 3-18 weeks), 2) the early follow-up period immediately after hCG administration (mean duration 5.0 ± 2.3 weeks; range 3-9 weeks), and 3) the second follow-up period (mean duration 6.1 ± 2.2 weeks; range 3-9 weeks). During this period, one of the boys could not participate due to the start of therapeutic administration of hCG.

For several reasons it was not possible to choose identical time intervals for each separate study period and, unfortunately, there were no data available on alkaline phosphatase activities during the second follow-up period.

The ulnar length was measured using a sensitive measuring device, developed and described by Valk (9-10), consisting of a fixing apparatus, a condylograph, and a measuring block. The fixing apparatus immobilizes the forearm in a reproducible manner in the position shown in figure 1A. The condylograph, shown in the same figure, consists of a metal cylinder fixed in a metal block allowing rotation around its longitudinal axis. The block is set in a metal frame with a spring enabling the observer to draw the cylinder under a reproducible pressure along the ulnar side of the right hand till the condylograph reaches the measuring point located between the styloid process of the ulna and the os triquetrum (figure 1A). When the measuring point is found, a resilient awl, placed in the center of the cylinder, can be moved downward to contact the measuring block (figure 1, B1 and C). This block (figure 1C) is composed of 100 metal plates of 0.1 mm tickness isolated from each other by 0.083 mm thin layers of a plastic. Each plate is connected to its own lamp, thus indicating a distance of 0.183

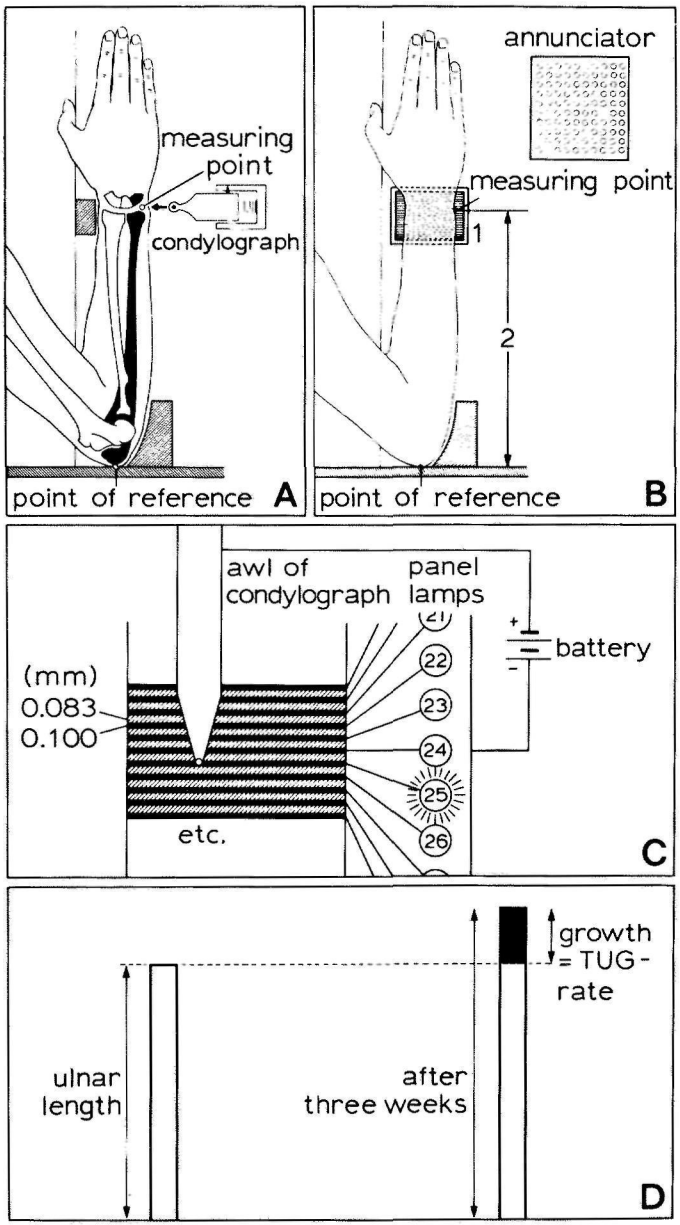

FIG. 1. The essentials of the ulnar length measuring technique.

mm to the next lamp. The lamps are collected in an annunciator in order to read out the results easily (figure 1B). Since the measuring range of the block itself is limited (1.83 cm), it can be moved in a slide and fixed in bores at intervals of 10,000 mm exactly enabling adaptation of the block to the length of the individual forearm. So changes in ulnar length can be expressed in lamps, and by multiplying with 0.183, in millimeters. The absolute ulnar length (figure 1B2) is determined by adding the calculated millimeters to the scaled distance between the block and the point of reference. Each ulnar length determination comprises six successive independent measurements, with a mean SE of 0.09 mm (the mean ulnar length at the start of the study was 238.58 ± 20.57 mm). Reliable detection of growth requires a change in ulnar length above approximately 0.2 mm. A period of three weeks has proved to be long enough to detect growth, since normal values for prepubertal and pubertal growth velocity amount to about 0.6 and 1.0 mm respectively. Growth in ulnar length was expressed 1) as the Three week Ulnar Growth rate (TUG-rate), calculated as shown in figure 1D and 2) as the increase in absolute ulnar length in millimeters. Growth in body height was measured using a standard device and was expressed as the three week body growth rate in centimeters. Growth in ulnar length has been demonstrated, at least over the long term, to correlate highly with growth in body height (11).

Plasma testosterone levels were measured using an antiserum generated in rabbits against 11-hydroxytestosterone hemisuccinate conjugated to albumin (15). Normal values for adult men are 314-1342 ng/100 ml. Serum alkaline phosphatase was measured using the Bessy and Lowry technique (16) adapted to automated analysis.

Unless otherwise stated, the mean values are given ± 1 SD.

STATISTICAL ANALYSIS

Differences in ulnar growth velocities during the respective periods were evaluated in two ways.

1) In case two successive periods were compared a direct graphical method was used to deal with the variable observation times. The three ulnar measurements (U_1, U_2 and U_3) were plotted against time. U_1 is the measurement at the beginning of the first period. U_2 is the one at the end of the first and the beginning of the second period, and U_3 is the measurement at the end of the second period. U_1 and U_3 are connected by a straight line indicating the average growth velocity during the total time period. The position of U_2 relative to this line is a measure for differences in growth velocity. If U_2 is above this line, the average growth velocity during the first period is larger than the velocity during the second period. U_2 below this line implies a larger velocity during the second period. A statistical test for differences in growth velocities between the two time periods includes Student's one-sample test for the whole group on the vertical distances between U_2 and the line U_1-U_3. This technique was used to test the differences in average growth velocities between time periods 1 and 2 and between time periods 2 and 3. To quantify these differences, the respective mean TUG-rates were used and tested by Student's T-test for paired observations.

2) To compare the differences in growth velocities during the two separate time periods the difference between the mean TUG-rates of the pretreatment period and the second follow-up was tested for the whole group using Student's test for paired observations.

Differences in plasma testosterone, serum alkaline phosphatase levels, and three week growth velocities in

body height during the different time periods of the study were also tested using Student's test for paired observations.

RESULTS

In figure 2 the changes in mean and individual TUG-rates, plasma testosterone levels, and serum alkaline phosphatase activities are depicted. Using the direct graphical method, a significant change in average growth velocity was assessed between the period before hCG loading and the early follow-up ($p < 0.01$) and between the early and the second follow-up period ($p < 0.05$). The mean TUG-rate increased from 0.40 ± 0.35 mm before hCG loading to 1.1 ± 0.64 mm during the early follow-up period ($p < 0.05$), whereas the mean TUG-rate decreased to 0.65 ± 0.28 mm during the second follow-up period ($p < 0.05$). The difference between the mean TUG-rates during the pretreatment period and during the second follow-up period lacked statistical significance ($0.05 < p < 0.10$).

No statistically significant differences were found between the three week growth velocities in body height during the respective periods (0.2 ± 0.2 cm before hCG loading, 0.2 ± 0.2 cm during the early follow-up period, and 0.4 ± 0.2 cm during the second follow-up ($p > 0.10$).

The mean plasma testosterone level increased from a basal level of 129 ± 126 to 818 ± 419 ng/100 ml immediately after hCG loading ($p < 0.01$). The mean plasma testosterone level during the second follow-up amounted to 213 ± 122 ng/100 ml and was not significantly different from the mean pretreatment value ($p > 0.10$). The mean serum alkaline phosphatase activity increased from 193 ± 46 U/liter in the period before hCG loading to 376 ± 115 U/liter during the early follow-up period ($p < 0.05$).

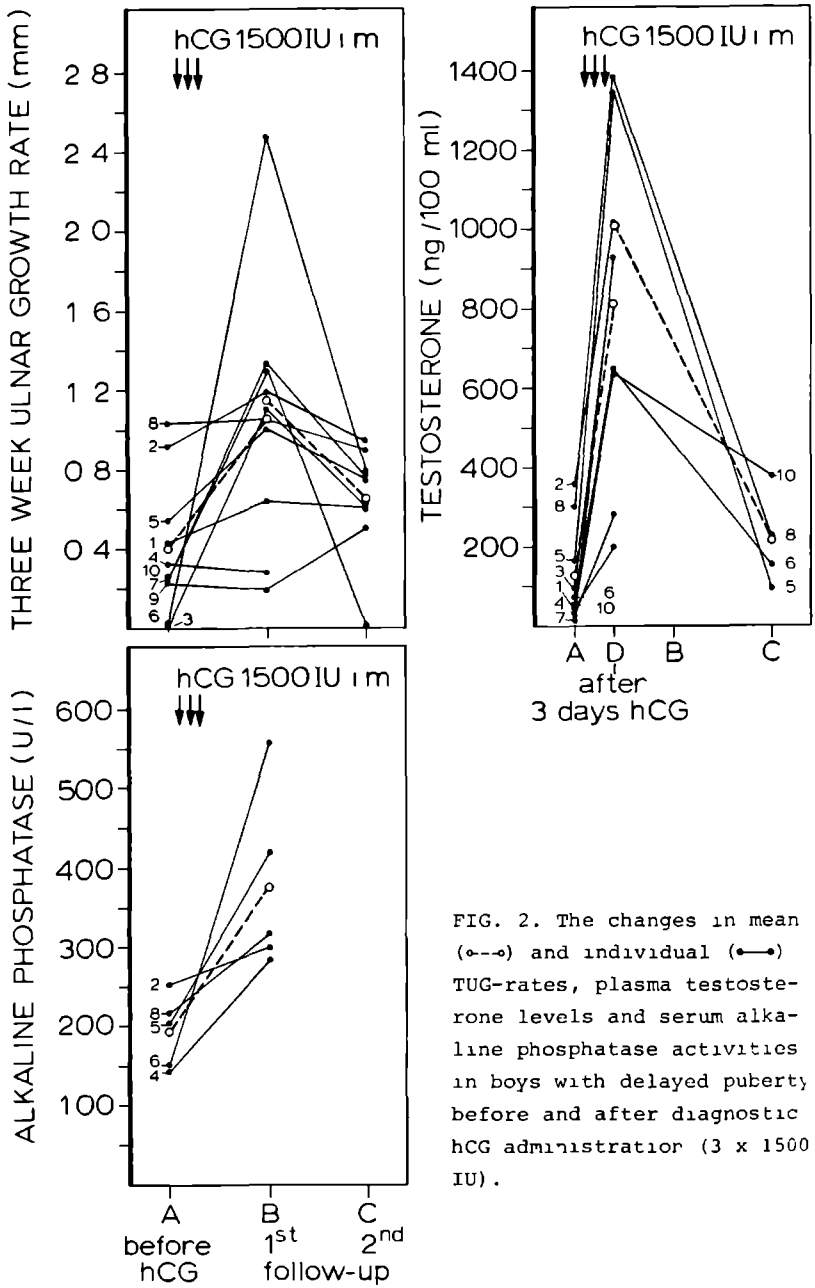

FIG. 2. The changes in mean (o--o) and individual (•—•) TUG-rates, plasma testosterone levels and serum alkaline phosphatase activities in boys with delayed puberty before and after diagnostic hCG administration (3 x 1500 IU).

DISCUSSION

Using a sensitive measuring device, hCG administration for three days was shown to increase ulnar growth velocity in boys with delayed puberty to a level of pubertal growth spurt (1.0 mm/three weeks), as described by Valk for normal Dutch boys (11). During the second follow-up, this growth promoting effect faded, reaching a prepubertal value of about 0.6 mm/three weeks as previously reported by this laboratory (9-11). This temporary growth accelerating effect of hCG was not detected by conventional body height measurements due to the high measurement error relative to the growth in body height during this short term growth study. The growth enhancement was accompanied by a huge increase in plasma testosterone levels and an almost doubling of the serum alkaline phosphatase activities in the early follow-up period.

To our knowledge, no data are available on the effect of hCG, administered on three consecutive days only, on growth and serum alkaline phosphatase activity. In a few other studies, a transient effect of hCG on growth velocity and serum alkaline phosphatase activity was assessed only after long term treatment (7-8).

The growth promoting effect of hCG administration is probably mediated by its androgen stimulating effect (17-22). Althought the precise mechanism is unknown, the present study illustrates that, by use of the not invasive ulnar length measuring technique, a growth promoting effect of diagnostic hCG administration can be detected in boys with delayed puberty closely coinciding with an early rise in plasma testosterone levels and serum alkaline phosphatase activities.

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CHAPTER 4

LACK OF DIFFERENCE IN GROWTH STIMULATING EFFECT BETWEEN WEEKLY SINGLE AND MULTIPLE HUMAN CHORIONIC GONADOTROPIN ADMINISTRATION IN BOYS WITH DELAYED PUBERTY

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SUMMARY

Using a non-invasive sensitive ulnar length measuring technique short term growth was studied in two groups of boys with constitutional delay in growth. In one group (A) a protocol of multiple hCG injections weekly was used (3 x 1500 IU), whereas the other (Group B) received a single dose of hCG weekly (1 x 1500 IU), both during six weeks.

The two hCG protocols appeared to be equally potent in stimulating Three week Ulnar Growth rates (TUG-rates), tripling the growth velocities from prepubertal to pubertal levels.

After stopping hCG treatment the mean TUG-rate decreased again to a post-treatment level that, taking both groups together, was significantly higher than the mean pretreatment TUG-rate.

During hCG administration mean body growth rates also rose significantly in the two groups. The extent of the changes, however, only allowed evaluation for the whole group in contrast to the changes in TUG-rates which far exceeded the limits of confidence in all but one boy.

Serum alkaline phosphatase activities (APA) increased significantly during hCG treatment and almost parallelled the increase in TUG-rates. The APA response (ΔAPA) in Group A, however, was unexpectedly higher than in Group B. After stopping hCG treatment the mean APA significantly decreased taking both groups together to an almost pretreatment level.

The data found indicate that a weekly single dose hCG regimen was sufficient and as effective as the weekly multiple injection protocol to stimulate TUG-rates to pubertal levels in the group of constitutionally delayed boys studied.

INTRODUCTION

Sex hormone treatment of constitutionally short stature in boys with delayed puberty has been discussed since Dorff in 1935 discovered the growth promoting effect of human chorionic gonadotropin (hCG) (1-5). Accelerated onset of growth spurt during androgen therapy was found indeed but also a possible reduction in final body height due to accelerated closure of the epiphyseal discs (6-7). However, Reiss et al. (2) and Kaplan et al. (4), treating constitutionally short boys with hCG and testosterone respectively, did not find evidence for premature epiphyseal closure, confirming earlier reports (8-9). Kaplan even suggested that the group treated reached a final height closer to the predicted height than the control group. Nevertheless, the risk of reduced final body height by androgen therapy in boys with delay in growth is still emphasized in literature. This added to reported adverse effects, led to reserve in hormonal treatment so that stimulation of growth is now only recommended in those cases where serious psychological problems arise (10-13).

However, in case therapy is necessary, there is no consensus about the kind of androgen stimulation - exogenous or endogenous -, the lowest effective dose and the way of administration to achieve the best results with lowest adverse effects. As to gonadotropins as growth promoting agent, recent research demonstrated that even diagnostic use hCG (1500 IU daily for three days) caused growth acceleration to pubertal levels for as long as six weeks (5). Furthermore Smals et al. (14) demonstrated that there was no significant difference in Leydig cell responsiveness after single or daily repeated hCG administration, due to relative refractoriness to subsequent gonadotropin administration for at least 48 hr after the priming dose (15-16).

Moreover, it has also been documented that one single dose of hCG may increase testosterone levels in boys with delayed puberty as long as 144 hr or even longer (14, 17-18).

These data led us to compare the growth promoting effect of the generally recommended protocol of weekly multiple hCG injections (19-22) and a weekly single dose hCG regimen in two groups of boys with constitutional delay in growth using the ulnar length measuring technique (5, 23-24).

MATERIALS AND METHODS

Two groups of boys with constitutional delay in growth participated in this study after obtaining informed parental consent. Eight boys were treated with 3 x 1500 IU hCG (Pregnyl^{R}) weekly im for six weeks (Group A) and nine boys with 1 x 1500 IU hCG weekly im for the same period (Group B).

Data on growth and development of both groups at the start of the study are tabulated in table 1. In all boys body height was below the 10th centile for Dutch boys (25). Mean bone age according to Greulich and Pyle (26) was retarded for an average of four years in the two groups. Although Group B contained boys younger, smaller and lighter the differences with Group A were not significant ($p > 0.10$).

The study was divided into three parts: before, during and after hCG administration each covering a time interval of six weeks. After assessing the growth promoting effect of hCG for each group separately the difference in response to weekly multiple (Group A) and single (Group B) hCG administration was evaluated. The effect of stopping the gonadotropin administration could be assessed in six boys of each group.

GROUP	n		AGE (yr)	BONE AGE (yr)	BODY HEIGHT (cm)	BODY WFIGHT (kg)	TANNER STAGE*	TESTOSTERONE (ng/100 ml)
A	8	mean	16.2 + 0.8	12.0 + 1.0	153.0 + 9.7	44.9 ± 9.0	G_{1-2}	56 ± 29
3x1500 IU hCG/weekly		range	15.0 - 17.0	11.0 - 14.0	135.3 - 166.4	35.0 - 58.2	P_{1-2}	24 - 107
B	9	mean	15.6 + 0.9	11.6 ± 1.4	148.0 + 6.5	40.2 + 7.5	G_{1-2}	56 ± 48
1x1500 IU hCG/weekly		range	14.5 - 17.0	10.0 - 14.0	138.0 - 159.7	29.8 - 51.4	P_{1-2}	23 - 126

* G = genital stage
P = pubic hair stage

TABLE 1. Characteristics on growth and development in two groups of boys with short stature and delayed puberty treated with two different hCG regimens for six weeks. No statistically significant differences in basic characteristics were found between the two groups.

Growth velocities were measured using the ulnar length measuring technique developed and described by Valk (23-24) and recently by van den Bosch et al (5). This technique enables accurate measurement of short term growth (5, 27-28). Each ulnar length determination comprises six successive independent measurements by the same observer. The mean of the SD of the samples in this study amounted to 0.20 mm implying a SE of 0.08 mm. Growth in ulnar length was expressed as the Three week Ulnar Growth rate in mm, i.e. TUG-rate, which actually reflects the change in ulnar length per three weeks.

Growth in body height was determined using the Harpenden stadiometer and expressed as the three week body growth rate in cm.

Blood for measurement of serum alkaline phosphatase activities was sampled before, during and after hCG loading. Serum alkaline phosphatase activities were measured using the Bessy and Lowry technique (29), adapted to automated analysis. Blood for measuring testosterone levels was sampled before and after hCG loading. Plasma testosterone was assayed after a paper chromatographic purification step using an anti-serum generated in rabbits against 11-hydroxytestosterone hemisuccinate conjugated to albumin (30). Unfortunately, blood for testosterone was sampled at different time intervals after the last injections in the two groups. Therefore these data did not allow appropriate comparison of actual Leydig cell stimulation and were excluded from the present study.

Mean values are given ± 1 SD.

STATISTICAL ANALYSIS

Statistical analysis was performed using Student's T-test for paired (P values are denoted by p) and unpaired data (P values are denoted as p*). The chosen level of statistical significance (two-sided) was $p = 0.05$.

RESULTS

the growth promoting effect of hCG administration (fig. 1)

In the two groups studied hCG administration caused a significant increase in ulnar growth velocity. The mean TUG-rates tripled, in Group A from a pretreatment value of 0.46 ± 0.30 mm to 1.37 ± 0.31 mm during hCG loading ($p < 0.001$) and in Group B from 0.35 ± 0.28 mm to 1.07 ± 0.34 mm ($p < 0.005$). In all boys of Group A and in eight out of nine boys of Group B the increase in TUG-rate during hCG treatment far exceeded the limit of confidence (3 x SE).

Mean body growth rates also increased significantly in the two groups, from 0.2 ± 0.1 cm before to 0.6 ± 0.3 cm during hCG administration in Group A ($p < 0.01$) and from 0.3 ± 0.2 cm to 0.6 ± 0.1 cm in Group B ($p < 0.005$).

comparison of the growth promoting effect of weekly single and multiple hCG administration (fig. 1)

There was no difference in mean pretreatment TUG-rates between the two groups ($p^* > 0.10$) and although there was a tendency for a higher mean TUG-rate in Group A during hCG administration as compared to Group B, the difference also lacked statistical significance ($0.10 > p^* > 0.05$).

The mean increase in TUG-rate (Δ TUG-rate) during hCG loading in Group A (0.91 ± 0.35 mm) was not significantly different from the Δ TUG-rate in Group B (0.72 ± 0.52 mm) ($p^* > 0.10$).

The same lack of statistical significance was found for the differences in absolute body growth rates before and during hCG administration as well as for the difference in the increase in the mean body growth rates (Δ body growth rate) between both groups (0.4 ± 0.3 cm for Group A and 0.3 ± 0.2 cm for Group B) ($p^* > 0.10$).

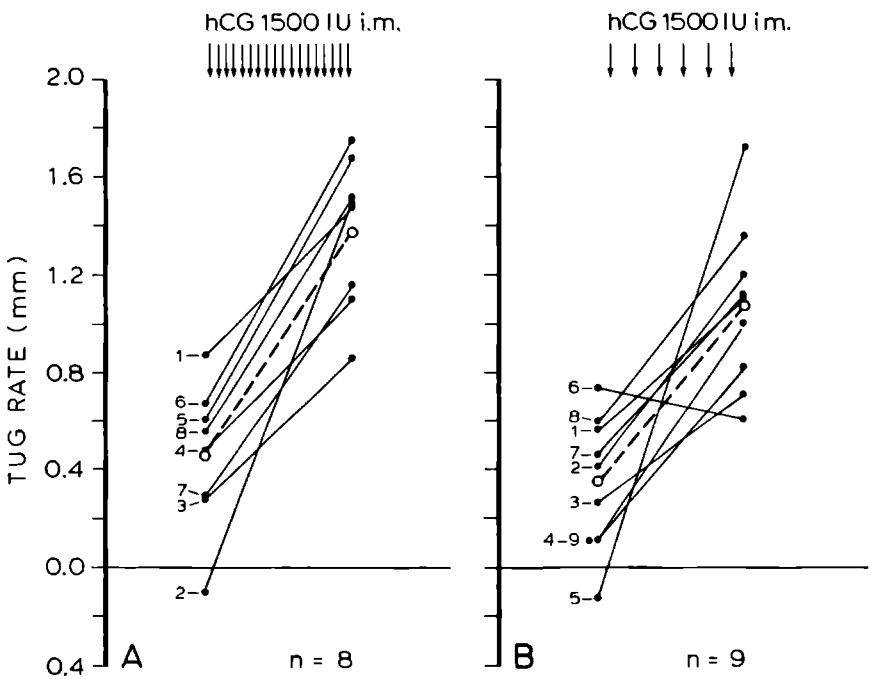

FIG. 1. The changes in mean (o---o) and individual (•——•) Three week Ulnar Growth rates (TUG-rates) during six weeks of a weekly multiple (A) and single dose hCG regimen (B) in boys with delayed puberty. The numbers refer to the individual patients.

the effect of stopping hCG injections (fig.2)

After stopping drug therapy the mean TUG-rates decreased to almost equal levels: in Group A from 1.45 ± 0.27 to 0.76 ± 0.21 mm ($p < 0.005$) and in Group B from 1.07 ± 0.40 to 0.75 ± 0.45 mm ($p < 0.10$).

The mean pretreatment TUG-rate in Group A (0.58 ± 0.19 mm) was significantly lower than the mean post-treatment TUG-rate ($p < 0.05$). For Group B no such difference was detected but taking the two groups together a significantly higher mean post-treatment TUG-rate was found (0.48 ± 26 vs 0.76 ± 0.34 mm) ($p < 0.05$).

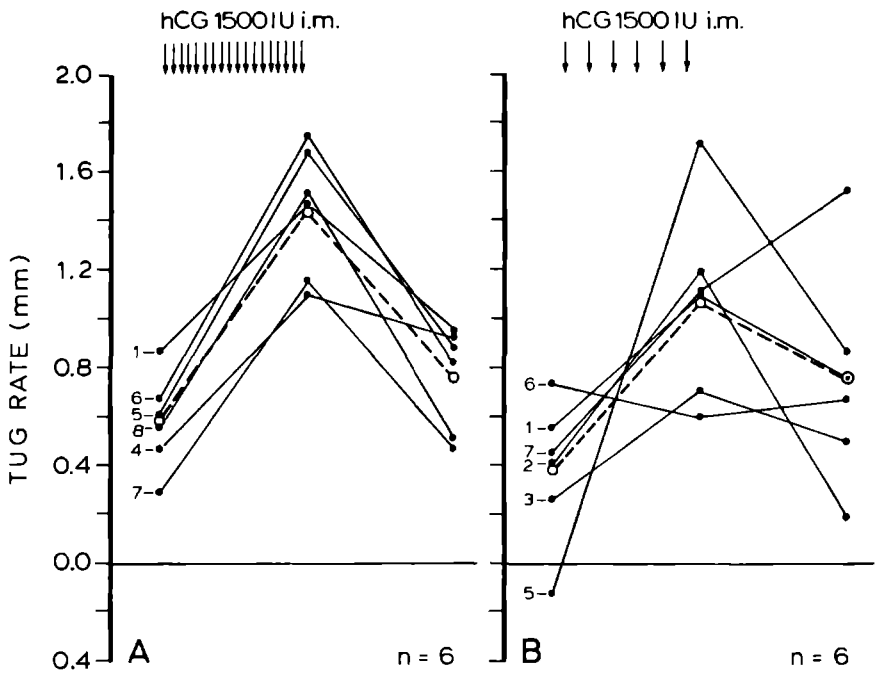

FIG. 2. The changes in mean (o----o) and individual (•——•) Three week Ulnar Growth rates (TUG-rates) in the six week periods during and after a weekly multiple (A) and single dose hCG regimen (B) in boys with delayed puberty. The numbers refer to the individual patients.

No systematic differences were found in changes in body growth rates after stopping hCG injections in either group ($p > 0.10$).

the effect of hCG administration on serum alkaline phosphatase activities (fig. 3)

In figure 3 the changes in the mean and individual serum alkaline phosphatase activities (APA) are depicted in relation to their respective TUG-rates, showing a significant increase in APA during hCG administration in Group A from 167 ± 23 to 273 ± 37 U/l ($p < 0.005$) and in Group B from 201 ± 32 to 256 ± 52 U/l ($p < 0.01$).

Comparing the absolute APA, the pretreatment values in Group A tended to be lower than in Group B, but the difference was not statistically significant ($0.10 > p^* > 0.05$). During hCG treatment the enzyme levels were almost similar in the two groups. Remarkably, the increase in APA (Δ APA) in Group A during hCG administration was nearly twice as high as in Group B ($p^* < 0.02$), whereas the TUG-rates did not differ significantly.

After stopping hCG treatment the decrease of APA was only significant taking the two groups together (from 270 ± 46 to 238 ± 62 U/l, $n = 9$, $p < 0.05$). The mean post-treatment APA did not differ from the mean pretreatment value (206 ± 36 U/l) in these nine boys ($p > 0.10$).

DISCUSSION

Human chorionic gonadotropin is widely used as a growth promoting agent in boys with short stature and delayed puberty. Doses ranging from 400 to 6000 IU twice or three times weekly or even daily during three to six months and

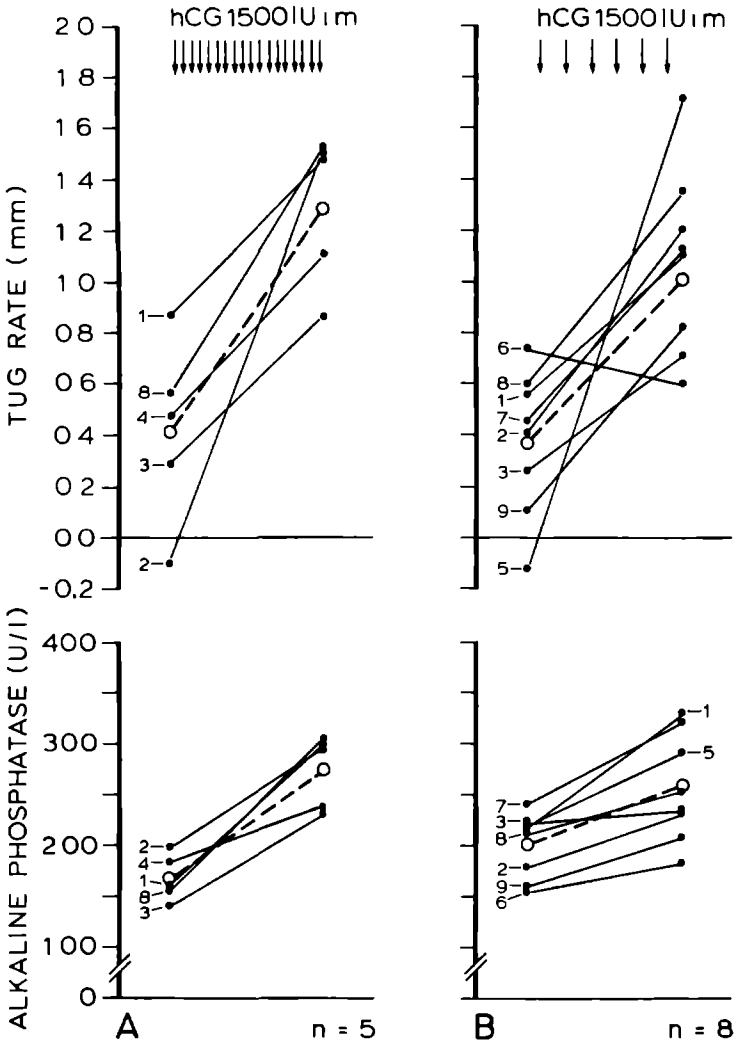

FIG. 3. The changes in mean (o----o) and individual (•——•) Three week Ulnar Growth rates (TUG-rates) and the concomitant changes in serum alkaline phosphatase activities during six weeks of a weekly multiple (A) and single dose hCG regimen (B) in boys with delayed puberty. The numbers refer to the individual patients.

longer have been recommended (2, 19-22, 31-32). However, using the non-invasive ulnar length measuring technique, a persistent growth promoting effect could be demonstrated even after diagnostic (1500 IU for three days) hCG administration (5).

The present study, using the same sensitive technique, compared the effect of a weekly multiple (3 x 1500 IU) and single dose (1 x 1500 IU) therapeutic hCG regimen on short term growth in boys with delayed puberty. During the two protocols gonadotropin administration increased the ulnar growth velocity within six weeks from prepubertal values to levels similar or even exceeding the physiologically occurring pubertal growth spurt (33). Remarkably, both drug regimens proved to be equally potent in increasing growth velocity by tripling the basal values.

The mean body growth rates also increased significantly during hCG administration in the two groups. However, in contrast to the changes in individual TUG-rates, which far exceeded the limit of confidence, the changes in body growth rate were too small in relation to the error of measurement (34) to allow evaluation in individual boys.

After stopping hCG therapy the ulnar growth velocities sharply decreased in the two groups to almost identical levels during the following six weeks. The post-treatment mean ulnar growth velocity was significantly higher than the pretreatment value for both groups together, confirming data of Reiss using a daily hCG injection regimen for longer periods (2).

In both the single and multiple injection protocol changes in serum alkaline phosphatase activities (APA) after hCG administration almost parallelled the change in ulnar growth rate. However, no correlation was found between the two parameters. In both groups APA rose to about similar values though the increase was unexpected-

ly more pronounced in the multiple injection group, despite similar acceleration in growth velocity. After stopping hCG treatment APA slightly fell to pretreatment levels. This increase in APA in response to hCG administration mimics the physiologically occurring pubertal increase which is found to be maximal immediately before peak height velocity (35). Gonadotropin induced testosterone and/or estrogen secretion in concert with enhanced growth hormone release (36-37) may account for the temporarily increased APA during hCG therapy.

The data presented so far indicate that weekly single hCG administration was as effective as the multiple injection therapy in achieving physiological pubertal growth velocities in the two groups of boys with delayed puberty studied here. This lower dose of hCG might decrease the risk of dissociation between skeletal maturation and growth enhancement as was already demonstrated for testosterone therapy, since this phenomenon is apparently dose dependent (3, 7).

The lack of difference in growth promoting effect between the two protocols might be explained by the assumption that single as well as multiple weekly gonadotropin administration raises circulating androgen levels in delayed puberty long enough (14, 17-18) and high enough to exceed a critical level which in cooperation with growth hormone warrants growth stimulation. Refractoriness of the Leydig cell to subsequent hCG administration after hCG priming might account for the lack of an additional effect on growth velocity after rapidly repeated hCG injections (14-16).

Whatever the precise mechanism may be, the results found illustrate that a therapeutic regimen of 1 x 1500 IU hCG weekly for six weeks was sufficient to trigger the chain of metabolic events leading to pubertal-like

growth acceleration in the group studied.

Scrutinizing the data on growth enhancing effect of diagnostic hCG administration (5) one is struck by the similarity of the responses in ulnar growth velocities and APA patterns in both studies indicating that even short lasting Leydig cell stimulation by hCG is sufficient to cause a similar growth acceleration persisting for five to six weeks or even longer. In view of the Leydig cell refractoriness after hCG priming it might even be possible that only one single injection of hCG evokes such sustained response.

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CHAPTER 5

THE EFFECT OF LOW DOSE ESTROGENS ON SHORT TERM GROWTH AND CONCOMITANT BIOCHEMICAL PHENOMENA IN GIRLS WITH TALL STATURE

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SUMMARY

Using a simple non-invasive ulnar length measuring technique a 70 to 80% decrease in ulnar growth velocity was found during one interval of nine weeks of low dose ethinylestradiol administration (0.050 mg daily) in girls with tall stature. This decrease in ulnar growth velocity was found to be statistically significant within six and even three weeks after starting estrogen loading whereas the change in body growth velocity was only significant after nine weeks. After stopping estrogen administration, ulnar growth velocities increased again but to values tending to be lower than before ethinylestradiol loading.

Serum alkaline phosphatase activities and plasma inorganic phosphorus and calcium levels also decreased significantly during estrogen therapy within nine weeks. The results found illustrate that the measuring technique used enables evaluation of the short term effect of hormonal treatment on growth and thereby related biochemical phenomena.

INTRODUCTION

Since the first report on the effect of estrogen administration on growth in girls with tall stature (1), many authors discussed the various aspects of estrogen therapy such as the effect on final body height, dose and nature of estrogen used, age of initiation and the mechanism of action, which is essentially still unknown (2-9). Especially the last years a revival in this discussion is noticeable (10-16).

The present study deals with another aspect of estrogen administration. As published before, the accurate non-invasive measuring technique developed by Valk enables the study of short term growth of the human ulna (17-21). Therefore it was thought worthwhile to study the short term effect of low dose estrogen administration on growth in both ulnar and body length and on the concomitant changes in serum alkaline phosphatase activities and plasma calcium and inorganic phosphorus levels in girls with constitutionally tall stature.

MATERIALS AND METHODS

Thirteen girls with tall stature participated in this study. The mean age (± SD) was 13.1 ± 1.7 yr (range 11.5 - 17.0 yr), whereas the skeletal age, according to Greulich and Pyle (22) was 13.3 ± 1.7 yr (range 11 - 15.5 yr). Mean body height amounted to 174.4 ± 6.4 cm (range 161 - 184 cm) and was above the 97th percentile for Dutch children (23) in eleven girls. Most of the girls were in Tanner stage III-IV. Only three had menarche before estrogen was administered. After excluding endocrine disorders and diagnosing tall stature as constitutional, all girls were

given ethinylestradiol (Lynoral^{R}, 0.050 mg per day orally) during a period of three to six months.

The growth of the ulnar length was measured using a sensitive device developed and described by Valk (17-18) and recently summarized by van den Bosch et al. (21).

Each ulnar length determination comprised six successive independent measurements. The mean SD of the determinations in this study was 0.20 mm implying an SE of 0.08 mm. Reliable detection of growth requires a change in ulnar length above approximately 0.20 mm. A period of three weeks has proved to be long enough to detect growth, since normal values for prepubertal and pubertal ulnar growth velocity amount to 0,60 and 1.00 mm per three weeks respectively. Since the essential of the method is the measurement of the change in ulnar growth velocity rather than the absolute ulnar length, growth is expressed as the Three week Ulnar Growth rate (TUG-rate).

Body height was measured using a standard device and was expressed as the three week body growth rate in cm. Growth in ulnar length has been demonstrated to correlate highly with growth in body height, the ratio being one to five respectively (19).

Since a period of nine weeks was considered to be sufficient to detect significant changes in both ulnar and body length, the mean growth velocity was assessed in all girls over one period of nine weeks before and during estrogen administration as shown in figure 1. However, in order to detect the time interval in which changes became first apparent the mean growth velocity was also determined over an interval of six weeks (n=10) and three weeks (n=3) immediately preceding and during the estrogen loading (figure 1).

After three to six months in some of the girls the estrogen administration was stopped. This enabled compari-

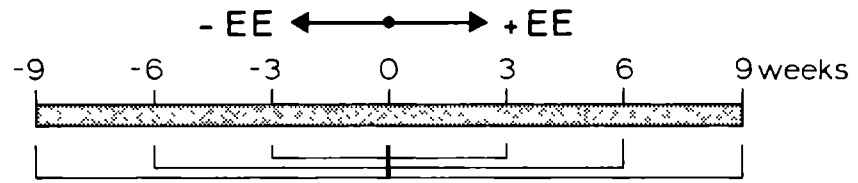

FIG. 1. Diagram outlining the study period of nine weeks before and during ethinylestradiol (EE) administration in thirteen girls. Within this study period two intervals were chosen of six (n=10 girls) and three weeks (n=3 girls) respectively in order to detect in which time interval the effect of estrogens on growth became first noticeable.

son of the growth velocities over a time interval of nine and six weeks during and after estrogen administration in a way similar to the procedure depicted in figure 1. No sufficient data were available over the three week intervals immediately before and after stopping.

In order to assess the concomitant biochemical changes, blood for the determination of plasma calcium and phosphorus levels and serum alkaline phosphatase activities was sampled before and nine weeks after ethinylestradiol administration. Plasma calcium and phosphorus levels were determined using routine laboratory techniques. Serum alkaline phosphatase activities were measured using the Bessy and Lowry technique adapted to automated analysis (24).

The mean values are given ± 1 SD.

STATISTICAL ANALYSIS

Differences in ulnar and body growth velocities during the respective periods (before-during and during-after estrogen loading) were tested using Student's T-test for paired observations. The growth velocities before and af-

ter ethinylestradiol administration were compared in the same way.

Differences in plasma calcium and phosphorus levels and serum alkaline phosphatase activities before and during estrogen loading were also tested using the paired Student's T-test.

RESULTS

In figure 2 the changes in the mean and individual TUG-rates during the nine week interval are depicted. The left panel shows the significant decrease of the TUG-rate from a pretreatment value of 0.59 ± 0.29 mm to 0.22 ± 0.27 mm during ethinylestradiol loading ($p < 0.001$). The right panel refers to the significant increase in TUG-rate from 0.04 ± 0.17 mm during to 0.22 ± 0.05 mm after stopping ethinylestradiol administration ($p < 0.05$). The decrease in the mean three week body growth rate from 0.33 ± 0.24 cm before to 0.14 ± 0.26 cm during estrogen administration was also statistically significant ($p < 0.05$). No significant change in body growth was found after stopping the ethinylestradiol loading.

In figure 3 the changes in the mean and individual TUG-rates during both the six and three week intervals are similarly depicted. The left panel refers to the changes during the six week periods, showing the statistically significant decrease in TUG-rate from 0.57 ± 0.27 mm before to 0.13 ± 0.28 mm during ethinylestradiol administration ($p < 0.001$). Although there was a tendency, the increase in ulnar growth velocity after stopping ethinylestradiol treatment lacked statistical significance ($0.10 > p > 0.05$). The right panel refers to the significant decrease in mean ulnar growth velocity from

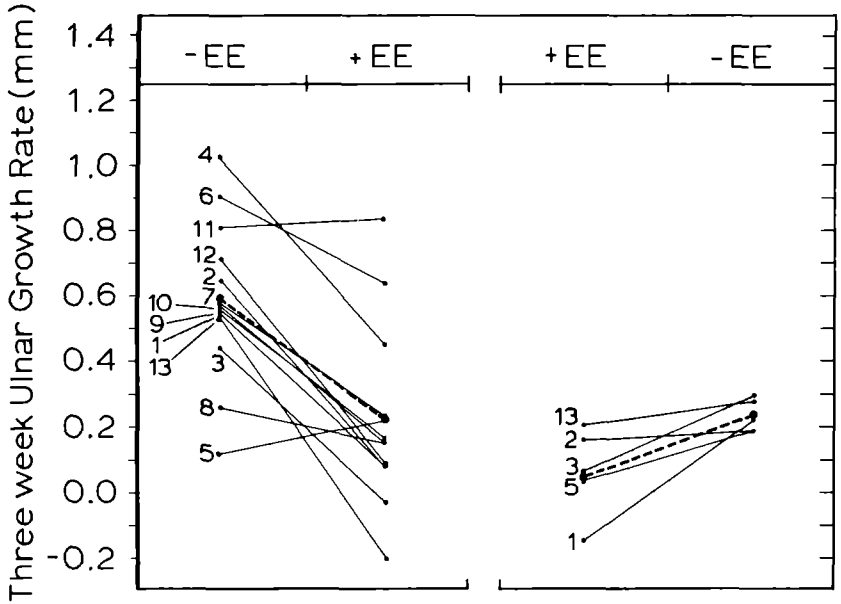

FIG. 2. The decrease in the mean (•--- •) and the individual (•——•) TUG-rates during the period of nine weeks of ethinylestradiol (EE) administration (Lynoral^{R}, 0.050 mg daily) (left panel). The right panel refers to the increase in mean and individual TUG-rates after stopping EE loading in five girls. The numbers indicate the individual girls.

0,43 ± 0.23 mm before to 0.01 ± 0.24 mm during three weeks of ethinylestradiol administration ($p < 0.05$) and the only observation of an increase within three weeks after stopping. No significant changes in three week body growth velocity could be demonstrated during either period.

Comparing the mean ulnar growth velocities before starting (0.46 ± 0.20 mm, n=5) and after stopping estrogen loading (0.22 ± 0.05 mm, n=5) the latter tended to be lower ($0.10 > p > 0.05$).

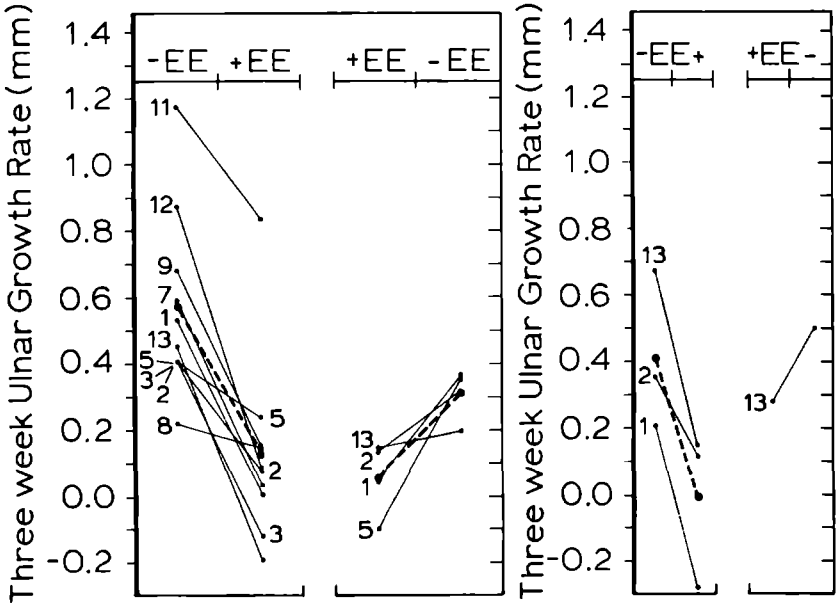

FIG. 3. The left panel shows the increase in the mean (•----•) and the individual (•——•) TUG-rates during six weeks of ethinylestradiol (EE) treatment and the increase after stopping ethinylstradiol loading. The right panel similarly depicts the decreases and increase during and after three weeks of ethinylestradiol administration. The numbers indicate the individual girls.

In figure 4 the changes in the mean and individual TUG-rates are depicted with the concomitant changes in serum alkaline phosphatase activities, calcium and inorganic phosphorus levels. The serum alkaline phosphatase activities changed significantly from 270 ± 160 U/l before to 199 ± 133 U/l during ethinylestradiol administration ($p < 0.01$, n=11). Similarly the plasma calcium and phosphorus levels decreased significantly during therapy from respectively 2.41 ± 0.09 to 2.32 ± 0.05 mmol/l ($p < 0.05$, n=10) and from 1.49 ± 0.19 to 1.36 ± 0.20 mmol/l ($p < 0.05$, n=10).

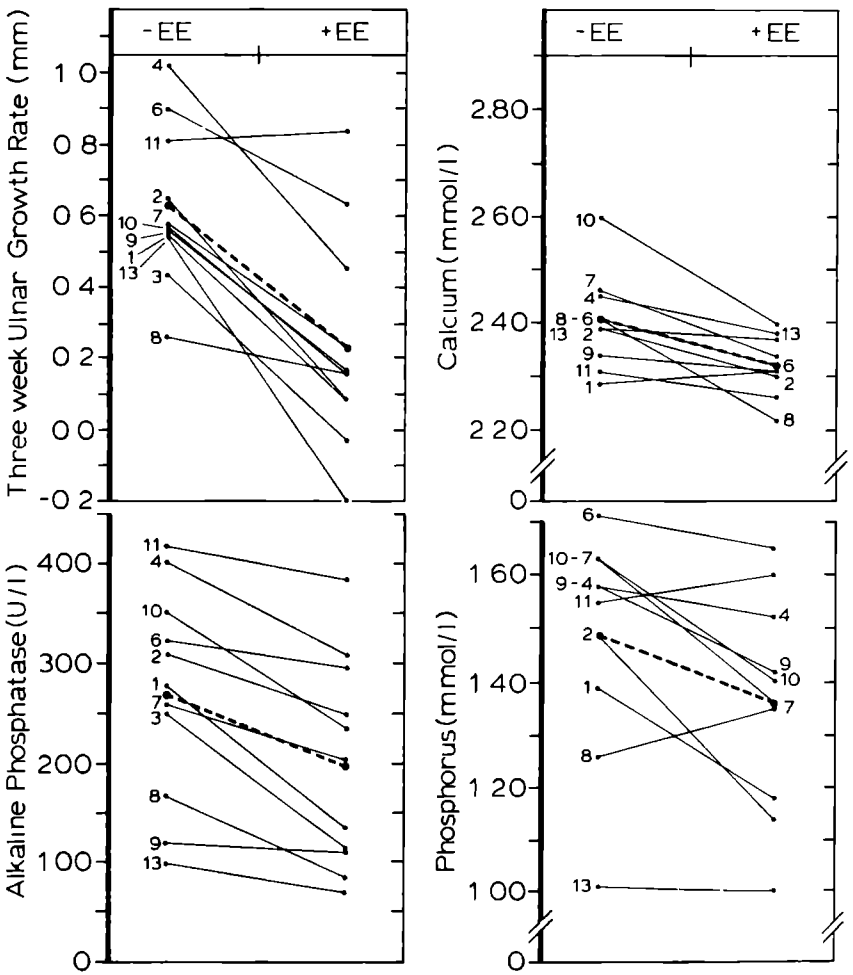

FIG. 4. The decrease in the mean (•----•) and the individual (•——•) TUG-rates in relation to the concomitant changes in serum alkaline phosphatase activities and plasma calcium and inorganic phosphorus levels during the nine week period of ethinylestradiol (EE) treatment. The numbers indicate the individual girls.

DISCUSSION

Using a sensitive measuring device a 70 to 80% decrease in TUG-rate was observed even within three weeks of rather low dose ethinylestradiol administration in constitutionally tall girls. Using a standard device a significant change in body height growth velocity could only be detected after nine weeks of estrogen treatment.

This suppressive effect of estrogens on body height has been amply reported in literature (vide supra) but the data published cover time intervals of three months or more. Wettenhall et al. (9) and Zachmann et al. (8), measuring body height with intervals of three to six months, observed a deceleration in body height growth velocity during estrogen therapy, however with doses considerably higher than used in the present study.

After stopping the estrogen loading the ulnar growth velocity increased again within three to nine weeks. This is in concordance with the proposed mechanism of action by which estrogens decelerate growth velocity by lowering plasma somatomedin levels (13). The post-treatment growth rates were somewhat lower than in the period immediately preceding estrogen administration. This decrease might be due to physiological fading of growth capacity with time but is more probably the direct consequence of ethinylestradiol therapy with its accelerating effect on the closure of the epiphyseal disc (8). However, the intended study period (of nine weeks) was too short to evaluate the effect on skeletal maturation.

Estrogen treatment induced a - to our knowledge not yet reported - significant fall in serum alkaline phosphatase activities and phosphorus levels in all girls within nine weeks after starting estrogen administration. As both parameters reflect bone growth activity (25-27) this

decrease is in concordance with the fall in TUG-rate. It is unlikely that the steep fall in both serum alkaline phosphatase activities and plasma inorganic phosphorus levels within the short time interval of nine weeks represents the physiologically occurring fall in these serum parameters in boys and girls after achieving peak height velocity (27). The admittedly small though statistically significant decrease in calcium levels might also be related to the diminished skeletal growth during estrogen therapy. Another explanation might be a depressive effect of estrogens on cholocalciferol synthesis (28) or simply on circulating albumin levels (29).

The present study illustrates that a non-invasive measuring technique as used in this study enables evaluation of the short term effect of hormonal treatment on growth and thereby related biochemical phenomena.

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CHAPTER 6

INSTANT GROWTH INHIBITION BY LOW DOSE ESTROGENS IN EXCESSIVELY TALL BOYS

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I.M. VALK
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SUMMARY

A major problem in androgen treatment of excessive height in boys is acceleration of growth velocity especially in the early stages of therapy. Estrogen treatment in tall girls, in contrast, instantly decelerates growth velocity, probably by its plasma somatomedin lowering effect. As estrogen administration in male subjects causes a similar somatomedin depression and immediate growth inhibition is also wanted in the treatment of excessive height in boys, the effect of short term low dose estrogen therapy (ethinylestradiol, Lynoral^{R}, 0.050 mg daily) on growth was studied in ten constitutionally tall boys.

During estrogen therapy Three week Ulnar Growth rate (TUG-rate) dropped instantly from 0.84 ± 0.42 mm to 0.33 ± 0.27 mm ($p < 0.02$) within six weeks. Three week body growth rate also changed significantly from 0.48 ± 0.23 cm to 0.12 ± 0.37 cm during estrogen loading ($p < 0.05$). The magnitude of the latter changes, however, allows only evaluation for the whole group, whereas changes in TUG-rates far exceeded the limits of confidence in most individual boys.

Growth deceleration during ethinylestradiol (EE) was accompanied by a significant decrease in serum alkaline phosphatase activities (from 299 ± 72 U/l before to 240 ± 79 U/l during EE, $p < 0.01$), plasma calcium (from 2.45 ± 0.06 mmol/l to 2.35 ± 0.05 mmol/l during EE, $p < 0.05$) and plasma testosterone levels (from 392 ± 128 ng/100 ml before to 27 ± 7 ng/100 ml during EE, $p < 0.005$). Within two months after stopping EE administration plasma testosterone levels were normal again (432 ± 282 ng/100 ml).

Testicular size was not affected. Mild reversible

gynecomastia, however, was present in all boys.

The results demonstrate an instant growth decelerating effect of low dose estrogen administration in tall boys reminiscent to the findings in tall girls under the same low dose regimen. Furthermore these data provide a theoretical base for combining androgens and estrogens in the early stages of treatment of excessive height in boys in order to antagonize the initial growth accelerating effect of androgens alone.

INTRODUCTION

In contrast to many reports on estrogen treatment of excessively tall girls (for review 1-2) only few papers deal with hormonal growth inhibition in tall boys (3-6). Like estrogens in tall girls, testosterone treatment in tall boys has proven to be successful in reducing final body height with regard to predicted height. Major problem, however, in testosterone therapy is acceleration of growth velocity in the early stages after starting androgen administration (7-8), particularly in the younger bone age group (5). Since serious psychological problems are the main indication for sex hormone treatment in most cases, acceleration of growth velocity is hardly acceptable when growth inhibition is wanted.

Estrogen therapy in tall girls, however, decelerates growth velocity instantly in most of the patients (9-10) even in low doses (11), probably by its somatomedin lowering effect (12-13). This decrease of plasma somatomedin by estrogens has also been demonstrated in male subjects (14-16). In contrast to estrogens, the effect of androgens on growth velocity is regarded to be independent of somatomedin and probably mediated by their anabolic action

per se (17-18). These latter actions may temporarily increase growth velocity in concert with elevated growth hormone levels (19-20), an undesired effect in the treatment of excessively tall boys. To overcome this initial growth accelerating effect of androgens - which occurs despite substantial peripheral aromatization of estrogens (21-22) - the effect of low dose estrogen therapy on short term growth was studied in boys with constitutional tall stature, using the sensitive ulnar length measuring technique.

MATERIALS AND METHODS

Ten constitutionally tall boys volunteered to participate in this study after obtaining informed parental consent. Data on growth and development at the start of the study are tabulated in table 1. Body height was above the 97th centile for Dutch boys (23) in all patients.

All boys received 0.050 mg ethinylestradiol (Lynoral^{R}) daily over a period varying from six weeks to six months.

In order to study the short term effect of ethinylestradiol growth velocities were assessed over a period of six weeks before and six weeks immediately after starting therapy. In nine boys the effect of stopping ethinylestradiol administration was evaluated measuring growth velocities six weeks before and after stopping.

Ulnar growth velocities were measured using the non-invasive ulnar length measuring technique developed and described by Valk (25-26) and recently by van den Bosch et al. (27) which enables accurate measurement of short term growth (11, 28-30). Each ulnar length determination comprised six successive independent measurements by the same observer. The mean SD of the samples in this study

amounted to 0.20 mm implying a mean SE of 0.08 mm. Growth in ulnar length was expressed as the Three week Ulnar Growth rate in mm, i.e. TUG-rate.

Growth in body height was determined using the Harpenden stadiometer and was expressed as the three week body growth rate in cm.

Blood for serum alkaline phosphatase activities, plasma calcium, phosphorus and testosterone levels was sampled before, during and after ethinylestradiol administration.

Serum alkaline phosphatase activities were measured using the Bessy and Lowry technique adapted to automated analysis (31). Plasma calcium and phosphorus were determined using routine laboratory techniques. Plasma testosterone was assayed after a paper chromatographic purification step using an antiserum generated in rabbits against 11-hydroxytestosterone hemisuccinate conjugated to albumin (32).

Mean values are given ± 1 SD.

	MEAN ± SD	RANGE
Calendar age	14.5 ± 1.37	12.5 - 16.0
Bone age* (yr)	13.5 ± 0.9	12.5 - 15.0
Body height (cm)	190 ± 6.9	176.5 - 203.4
Body weight (kg)	66.3 ± 8.2	52.9 - 77.0
Testicular size (cm)		
length	4 ± 1.1	1.5 - 5.5
width	3 ± 0.6	2 - 4
Tanner stage		II - V
Testosterone (ng/100ml)	404 ± 215	13 - 790

*According to Greulich and Pyle (24)

TABLE 1. Characteristics on growth and development in ten constitutionally tall boys at the start of the study.

STATISTICAL ANALYSIS

Differences in ulnar and body growth velocities, serum alkaline phosphatase activities, plasma calcium, phosphorus and testosterone levels between the respective study periods were tested using Student's T-test for paired observations. The chosen level of statistical significance (two sided) was $p = 0.05$.

RESULTS

the effect of ethinylestradiol (EE) on growth velocity (fig. 1)

The left panel of figure 1 reveals the changes in mean and individual TUG-rates during six weeks of EE administration (0.050 mg/daily). The mean TUG-rate decreased significantly from 0.84 ± 0.42 mm before to 0.33 ± 0.27 mm during EE treatment ($p < 0.02$). In eight of the ten boys the decrease in TUG-rate was above the limit of confidence (3xSE).

Three week body growth rate also decreased significantly from a mean pretreatment value of 0.48 ± 0.23 cm to 0.12 ± 0.37 cm during EE administration ($p < 0.05$). Body weight did not change significantly during EE loading ($p > 0.10$).

the effect of stopping ethinylestradiol (EE) administration (fig. 1)

The right panel of figure 1 refers to the changes in mean and individual TUG-rates after stopping the EE loading. Mean TUG-rate increased from 0.28 ± 0.32 mm during to 0.53

± 0.27 mm after stopping EE. Although there was a tendency this difference lacked statistical significance ($0.10 > p > 0.05$). Ulnar growth velocities before and after EE administration differed neither significantly ($p > 0.10$).

No changes in body growth rate and body weight were found during this part of the study ($p > 0.10$).

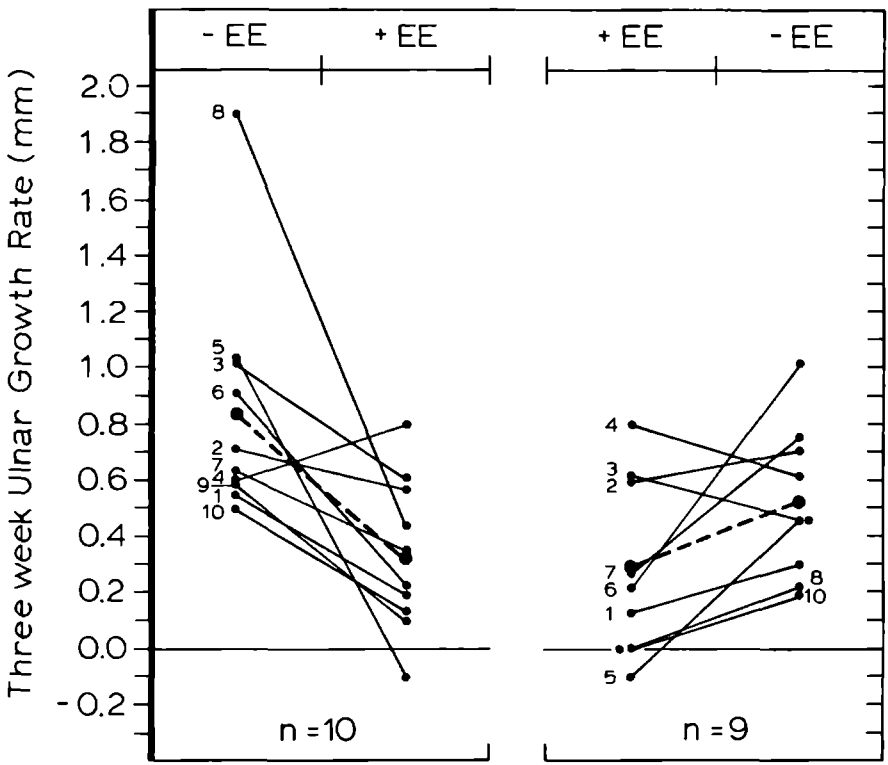


FIG. 1. The changes in mean (•----•) and individual (•——•) Three week Ulnar Growth rates (TUG-rates) in ten constitutionally tall boys. The left panel refers to the changes in TUG-rates during six weeks ethinylestradiol (EE) administration (Lynoral^{R}, 0.050 mg daily, n=10). The right panel reveals the changes in TUG-rates during six weeks after stopping EE in nine of them. Individual subjects are indicated by number.

the effect of ethinylestradiol (EE) on biochemical phenomena (fig. 2)

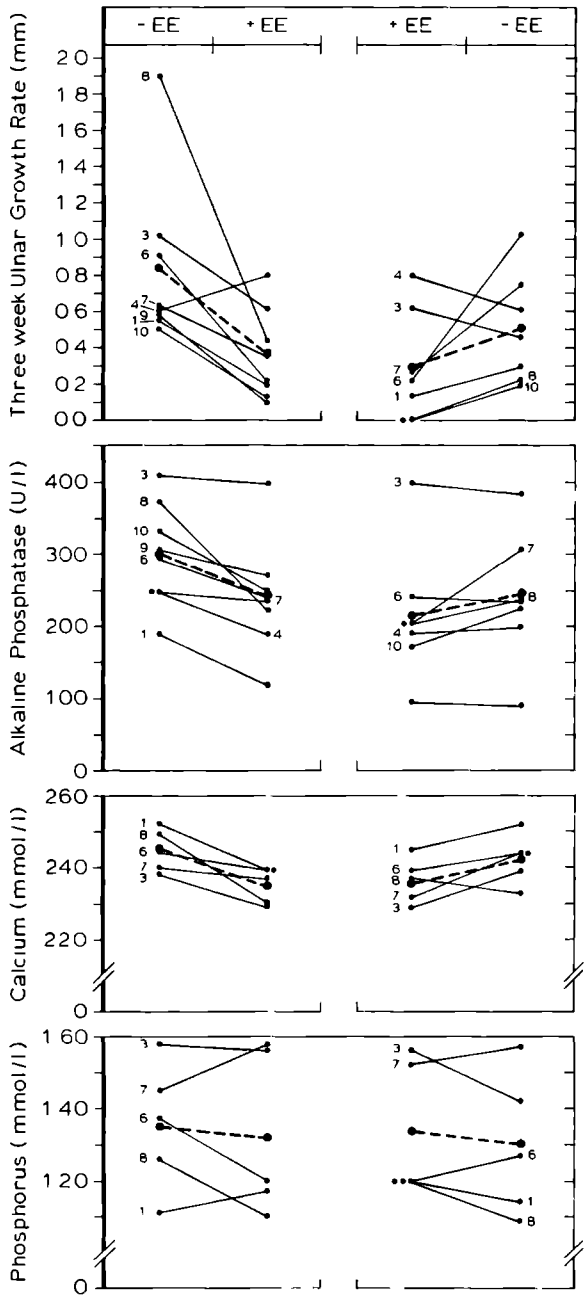
In figure 2 the changes in individual and mean serum alkaline phosphatase activities, plasma calcium and phosphorus levels are depicted in relation to the changes in TUG-rates. The left panel shows the changes after stopping EE.

Serum alkaline phosphatase activities decreased significantly from a mean level of 299 ± 72 U/l before to 240 ± 79 U/l during EE loading ($p < 0.01$, n=8). After stopping EE administration the mean phosphatase activities changed from 215 ± 92 U/l to 240 ± 90 U/l. This increment was not statistically significant ($p > 0.10$, n=7). Post-treatment phosphatase levels tended to be lower than pretreatment activities ($0.10 > p > 0.05$).

Mean plasma calcium decreased during EE loading from 2.45 ± 0.06 mmol/l to 2.35 ± 0.05 mmol/l ($p < 0.05$, n=5). After stopping EE the mean plasma calcium increased from 2.36 ± 0.06 to 2.42 ± 0.07 mmol/l. Although there was a tendency this increment was not statistically significant ($0.10 > p > 0.05$, n=5).

In contrast to plasma calcium and serum alkaline phosphatase activities, there were no significant changes in plasma phosphorus (1.35 ± 0.18 mmol/l before versus 1.32 ± 0.23 mmol/l during EE, and 1.34 ± 0.19 mmol/l during

FIG. 2. The changes in mean (•---•) and individual (•——•) serum alkaline phosphatase activities, plasma calcium and phosphorus levels in relation to the changes in Three week Ulnar Growth rate (TUG-rate) in constitutionally tall boys. The left panel refers to the changes during six weeks ethinylestradiol (EE) administration (Lynoral^{R}, 0.050 mg daily). The right panel illustrates the changes during six weeks after stopping EE. Individual subjects are indicated by number.


- EE
+ EE
+ EE
- EE
Three week Ulnar Growth Rate (mm)
20
18
16
14
12
10
08
06
04
02
00
Alkaline Phosphatase (U/l)
400
300
200
100
0
Calcium (mmol/l)
260
240
220
0
Phosphorus (mmol/l)
160
140
120
0

versus 1.30 ± 0.20 mmol/l after stopping EE loading, $p > 0.10$, n=5).

During EE treatment plasma testosterone levels fell from a pretreatment value of 392 ± 128 ng/100 ml to 27 ± 7 ng/100 ml ($p < 0.005$, n=5). Within two months after stopping EE loading testosterone levels had increased again to normal values (432 ± 282 ng/100 ml, $p < 0.05$, n=5). Two of these five boys were treated for six weeks, two for four months and one for six months.

the effect of ethinylestradiol (EE) on testicular size and mammary gland

In none of the ten boys testicular size was markedly reduced during EE therapy. The only change observed was a slight weakening of the testis in the boys treated for four to six months.

The effect on mammary gland tissue was more overt. Eight boys developed moderate gynecomastia within six weeks of EE administration, two boys only after longer treatment. Gynecomastia remained within acceptable limits for the patients and disappeared after stopping EE treatment within two months.

DISCUSSION

This study for the first time demonstrates the instant growth inhibiting effect of low dose estrogens in tall boys. The significant decrease of ulnar growth rate in response to this low dose of ethinylestradiol (EE) was almost identical to that found in tall girls (11). In both groups of tall girls and boys studied, body growth rate also decreased significantly during estrogen therapy. However, the

magnitude of the changes in body height allows only evaluation for the whole group, whereas the changes in TUG-rates far exceeded the limit of statistical confidence (3xSE) in nearly all individual youngsters.

After stopping EE administration ulnar growth rates tended to increase again, a phenomenon also observed in tall girls. Both the decelerating effect during EE and the acceleration after stopping EE might be in accordance with the proposed mechanism of action of estrogens on plasma somatomedin levels, which is well documented in literature for both sexes (12-16). A second mechanism accounting for the growth inhibition in these boys might be direct or indirect estrogen mediated suppression of Leydig cell function (33-36) illustrated by the overt fall of plasma testosterone levels to prepubertal values during treatment. Finally both mechanisms may simultaneously contribute to growth inhibition in boys. Mere growth hormone suppression as the cause of the instant growth inhibition can be ruled out since estrogens have been reported to even increase circulating HGH levels, probably due to the positive feedback of somatomedin reduction (15, 37).

This study on short term growth clearly demonstrates that also in tall boys low doses of estrogen are effective in instantly reducing growth velocity. Very recently the growth inhibiting effect of low dose estrogens was confirmed in a long term study in tall girls (38).

The decrease in growth rate during EE was also reflected by a significant reduction of serum alkaline phosphatase activities and plasma calcium levels, similar to that found in girls (11). In contrast to this latter study the plasma phosphorus levels did not change significantly in the boys, probably due to the smaller number of data available. The reduction of serum alkaline phosphatase activities during EE is opposite to the rise observed during

human chorionic gonadotropin (hCG) induced growth stimulation (27, 30) and therefore probably reflects diminished bone growth (39). The small but significant decrease in plasma calcium levels during EE might be explained by a depressive effect of estrogens on cholicalciferol synthesis (40) or on circulating albumin (41), but is more likely related to diminished skeletal growth during EE.

Testicular size was not affected during EE administration in this study and Leydig cell function was only temporarily suppressed as illustrated by the rapid recovery of plasma testosterone levels after stopping EE. An essential issue to be discussed is the hazard of potential infertility due to estrogen treatment in men. As in testosterone treatment (5, 10) estrogens cause oligo-azoöspermia (42-46) but under both drug regimens infertility has been reported to be reversible in animals (43-44) and men (5, 10, 42, 45-46) using even much higher doses of estrogens.

Although gynecomastia was manifest, it was mild and reversible in all boys.

Together these data illustrate that low dose estrogen therapy in boys results in instant growth deceleration which to our opinion is an important psychological advantage in the early management of tall stature in boys. Moreover the findings provide a theoretical base for temporarily combining androgens and estrogens in the early stages of treatment in tall boys in order to antagonize the initial growth accelerating effect of androgens alone.

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SUMMARY

SAMENVATTING

SUMMARY

This thesis describes the results of the application of a non-invasive ulnar length measuring technique in short term growth studies in tall and short statured adolescents treated with sex hormones.

The technique used enables accurate determination of growth in ulnar length over short time periods, mostly three weeks. Ulnar growth velocity is therefore expressed as the Three week Ulnar Growth rate (TUG-rate). Earlier it was demonstrated that growth in ulnar length highly correlates with growth in body height ($r = 0.83$), the ratio being one to five. However, the time period necessary for reliable detection of growth in body height is, despite higher velocity, three times longer. Moreover the method of the ulnar length measuring technique allows statistical evaluation for each individual TUG-rate found. In previous studies the average prepubertal and pubertal TUG-rates in girls and boys with normal body length appeared to be 0.6 mm and 1.0 mm respectively. Given a mean limit of confidence as low as 0.20 mm this ulnar length measuring technique enables reliable detection of changes in growth velocities over short periods. Therefore this technique was applied in response studies in children treated for excessive tall and short stature, aged between 11 and 17 yrs. None of these adolescents had apparent endocrine disorders, in fact all showed a variant of normal growth. The group studied was divided into two categories: i boys with serious delay in growth and sexual development. Body height was below the 10th centile for Dutch children. ii Boys and girls with excessively tall stature, exceeding the 97th centile.

Before the response to treatment could be studied in these patients, the problem of transient changes

in ulnar length during the day had to be solved, since such changes might influence the evaluation of short term growth.

Chapter two deals with this problem. During a period of three weeks the ulnar length of eleven boys was measured at seven set times between 08.00 h and 18.00 h. An overt diurnal rhythm was observed. Between 08.00 h and 12.00 h ulnar length decreased significantly for an average of 0.4 mm. During the afternoon no further significant changes in ulnar length could be detected. Despite this diurnal decrease a mean overall pubertal TUG-rate of 1.0 mm could be calculated. These findings suggested that growth in ulnar length occurs mainly during the night. Since changes in ulnar length during the morning are most pronounced patients should be measured in the afternoon and preferably at the same time in order to minimalize the influence of intra-daily variation of ulnar length on short term growth.

In chapter three short term growth was studied in ten boys with delayed puberty receiving human chorionic gonadotropin (hCG) for diagnostic purposes. This low dose of hCG increased ulnar growth velocity from low prepubertal to pubertal values for approximately 6 weeks. This growth promoting effect was preceded by an overt rise in plasma testosterone and associated with an almost doubling of serum alkaline phosphatase activities. These changes temporarily mimicked the physiologically occurring phenomena inherent to the initiation of the growth spurt.

In view of these results and the reported relative refractoriness of the Leydig cell to repeated hCG administration for 48 hours or longer after the priming dose, two therapeutic hCG regimens were compared. Chapter four reports on this study in which one group of boys with

delayed puberty received the usually recommended weekly multiple injection protocol (3 x 1500 IU/weekly), the other a weekly single dose of hCG (1 x 1500 IU), both during six weeks. The two hCG regimens appeared to be equally potent in stimulating TUG-rates, tripling the ulnar growth velocities from prepubertal to pubertal levels. After stopping hCG administration the mean TUG-rates again decreased but to a level significantly higher than before treatment. In contrast to the former study (chapter three) mean body growth rate increased significantly during hCG administration. However, the extent of the changes only allowed evaluation of the whole group, whereas changes in TUG-rates far exceeded the limit of confidence in all but one boy.

In this study serum alkaline phosphatase activities also increased during hCG treatment concomitant with the increase in TUG-rates. The results indicate that a weekly single dose of hCG was sufficient and as effective as the usually recommended weekly multiple dose protocol to stimulate TUG-rates to pubertal values.

In chapter five short term growth was studied in a group of excessively tall girls receiving a low dose of ethinylestradiol (0.05 mg daily). Using the ulnar length measuring technique it appeared that this low dose of estrogen decreased growth velocity significantly within six and even three weeks. Only after nine weeks the decrease in body growth rate became statistically significant. After stopping estrogen administration TUG-rates increased again.

Besides serum alkaline phosphatase activities, plasma calcium and phosphorus levels also changed significantly, decreasing during ethinylestradiol administration. The data found illustrate that even low doses of estrogens, as used in oral contraceptives, may decelerate growth

velocity and do so instantly.

Chapter six also deals with low dose estrogen therapy but - as was not yet reported before - in excessively tall boys. As for girls instant growth inhibition in tall boys is wanted and often needed. The usually recommended androgen therapy, however, accelerates growth in the early stages of therapy. In view of the data found in tall girls and reported theories on the mode of action of estrogens, ten boys with excessively tall stature were given a low dose of estrogen to study the effect on short term growth. TUG-rates decreased significantly and instantly and the changes found were almost identical to those observed in tall girls. Body growth rate significantly decreased too, but only for the whole group. After stopping estrogen treatment TUG-rates increased again in accordance with the proposed mechanism of action. As was expected alkaline phosphatase activities and serum calcium levels decreased significantly during ethinylestradiol administration, only the changes in phosphate levels lacked statistical significance. No serious or irreversible side effects were observed during this study. The results found illustrate that low doses of estrogens instantly decelerate growth velocity in tall boys which may be an important advantage in the early management of excessively tall stature.

SAMENVATTING

In dit proefschrift worden de resultaten beschreven van de toepassing van een niet-invasieve ulnalengtemeter voor de bestudering van groei op de korte termijn van te lange en te kleine adolescenten, die behandeld worden met geslachtshormonen.

De gebruikte techniek maakt een nauwkeurige bepaling van de toeneming in ulnalengte mogelijk binnen korte tijd, meestal drie weken. De verandering in ulnalengte wordt dan ook uitgedrukt als driewekelijkse groeisnelheid, de zgn. TUG-rate (Three week Ulnar Growth rate). Reeds eerder werd een nauwe relatie aangetoond tussen de toeneming in ulnalengte en de toeneming van de totale lichaamslengte, welke laatste ongeveer vijf maal zo hoog is als de groeisnelheid van de ulna. Ondanks deze hogere snelheid is het tijdsinterval, waarbinnen op betrouwbare wijze groei kan worden gemeten drie keer zo lang als bij de gebruikte techniek voor het meten van de ulna. Bovendien maakt deze wijze van meten het mogelijk iedere TUG-rate te toetsen aan een betrouwbaarheidsgraad. In voorgaande studies werd bij jongens en meisjes met een normale lichaamslengte een gemiddelde prepuberale en puberale toeneming van de ulnalengte gevonden van respectievelijk 0.6 mm en 1.0 mm per drie weken. Bij een gemiddelde betrouwbaarheidsgraad van 0.2 mm maakt dit een nauwkeurige meting van veranderingen in groeisnelheid binnen korte tijd mogelijk. De techniek werd daarom geschikt geacht om het effect van therapie te bestuderen bij te kleine en te lange adolescenten. Geen van deze kinderen had een endocrinologische afwijking en er kon bij allen gesproken worden van een variant van normale groei. De groep te kleine kinderen bestond uit jongens met een achterstand in groei en ontwikkeling. De lichaamslengte in deze groep was lager dan de 10e percentiel zoals die in

1965 voor normale Nederlandse kinderen werd gevonden door van Wieringen en medewerkers. De groep zeer lange adolescenten bestond uit jongens en meisjes, wier lichaamslengte de 97e percentiel overschreed.

Voordat echter het effect van therapie op de groei van deze kinderen kon worden bestudeerd diende het verschijnsel van de veranderingen in ulnalengte gedurende de dag nader te worden onderzocht.
Daarvoor werd gedurende een periode van drie weken telkens op zeven vaste tijdstippen tussen acht uur 's morgens en zes uur 's avonds de ulnalengte gemeten bij elf jongens. In hoofdstuk twee worden de resultaten van deze studie beschreven. Een duidelijk dagritme kon worden aangetoond. Tussen acht en twaalf nam de ulnalengte met 0.4 mm gemiddeld significant af. Gedurende de middag werden geen significante veranderingen gevonden. Opmerkelijk is, dat deze vermindering van de ulnalengte gedurende de dag optrad ondanks een gemiddelde puberale groeisnelheid van 1.0 mm per drie weken. Dit suggereert, dat groei van de ulna voornamelijk gedurende de avond en/of nacht plaats vindt.
Gezien de snelle daling van de ulnalengte 's morgens en de relatief stabiele lengte 's middags verdient het aanbeveling de patiënten 's middags te meten bij voorkeur op dezelfde tijd om eventueel storende invloeden van dit dagritme op de groeimetingen te minimaliseren.

In hoofdstuk drie wordt de korte-termijn-groei van jongens met een vertraagde puberteit beschreven, die om diagnostische redenen humaan choriogonadotrofine (hCG) kregen toegediend. Deze kortdurende toediening van hCG leidde tot een duidelijke toeneming van de plasmatestosteronspiegels en een significante versnelling van de groei van de ulna van laag prepuberale tot puberale waarden. Daarnaast trad er een verdubbeling van de alka-

lische fosfatase-activiteit in het bloed op. Tesamen weerspiegelen deze veranderingen de gebeurtenissen welke normaliter bij het begin van de groeispurt kunnen worden waargenomen.

Gezien deze bevindingen en de recente publicaties, wijzend op een relatief verminderde gevoeligheid van de Leydig cel voor snel herhaalde hCG injecties, werd het van belang geacht het effect van twee door ons gebruikte therapeutische hCG doseringen op de korte-termijn-groei te vergelijken. Hoofdstuk vier beschrijft deze studie, waarín één groep jongens met een vertraagde puberteitsontwikkeling de algemeen aanbevolen dosering van drie hCG injecties per week kreeg; een andere, vergelijkbare groep kreeg slechts één injectie hCG per week, beide gedurende zes weken. De twee doseringen bleken gelijkelijk in staat de groei te versnellen van laag prepuberale naar puberale waarden. Na het stoppen van de hCG toediening daalde de groeisnelheid weer, hoewel deze op een significant hoger niveau bleef dan voor de behandeling.

In tegenstelling tot de vorige studie veranderde de groeisnelheid van de lichaamslengte in dit onderzoek wel significant gedurende de hCG toediening. De toeneming was echter van dien aard, dat deze alleen voor de hele groep significant was, terwijl de veranderingen in TUG-rates de betrouwbaarheidsgrens ver overschreden bij alle jongens op een na.

Ook in deze studie nam de alkalische fosfatase-activiteit in het bloed significant toe gedurende de therapie, waarbij de stijging praktisch gelijke tred hield met de toeneming in TUG-rates.

De resultaten tonen aan dat een dosering van één injectie hCG per week even effectief blijkt als de gewoonlijk aanbevolen dosering van drie injecties per week om een

puberale groeisnelheid te bewerkstellingen.

In hoofdstuk vijf wordt een groep meisjes beschreven, die een lage dosis oestrogenen ontvingen als behandeling van hun overmatige groei. Er werd een significante daling van de groeisnelheid van de ulna waargenomen binnen zes en zelfs binnen drie weken na het begin van de toediening van oestrogenen. De afname van de groei in lichaamslengte werd echter pas na negen weken statistisch significant. Na het stoppen van de oestrogenen medicatie nam de gemiddelde TUG-rate weer toe, maar bleef onder het niveau van de snelheid vóór therapie.
Tegelijk met de afnemende groeisnelheid namen ook de alkalische fosfatase-activiteit, de calcium- en fosforspiegels in het bloed gedurende het toedienen van oestrogenen significant af.
Deze bevindingen laten zien dat ook een lage dosis oestrogenen, zoals gebruikt in orale contraceptiva, een groeiremmend effect heeft, welk effect onmiddellijk na start van de toediening optreedt.

In hoofdstuk zes wordt eveneens het effect van een lage dosis oestrogenen op de groei beschreven, maar nu - hetgeen nog niet eerder werd gedaan - bij bovenmatig lange jongens. Evenals bij meisjes is ook bij deze jongens vaak een onmiddellijke groeiremming gewenst. De gebruikelijke therapie met androgenen is in dit opzicht dan ook paradoxaal daar deze aanvankelijk de groei stimuleert.
Gezien de resultaten van het onderzoek bij meisjes en de publicaties betreffende het werkingsmechanisme van oestrogenen werden tien te lange jongens behandeld met een lage dosis ethinyloestradiol. Binnen zes weken trad een significante daling van de groeisnelheid van de ulna op, identiek aan die gevonden bij meisjes. Weliswaar nam ook de groei in lichaamslengte af, maar deze

afname was alleen statistisch significant voor de hele groep. Na staken van de toediening van oestrogenen nam de groeisnelheid weer toe, overeenkomstig het beschreven werkingsmechanisme.
Evenals bij meisjes daalden ook bij deze jongens de alkalische fosfatase-activiteit en het plasmacalcium statistisch significant. Dit gold niet voor de daling van het fosfaatgehalte.
Tijdens en na de toediening van deze lage dosis oestrogenen werden geen ernstige of blijvende bijwerkingen gezien.
De resultaten tonen aan, dat een directe groeiremming verkregen wordt met behulp van oestrogenen bij te lange jongens, hetgeen een belangrijk psychologisch voordeel kan zijn bij het begin van de behandeling.

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Graag wil ik een ieder bedanken die bij het tot stand komen van dit proefschrift betrokken is geweest. Met name wil ik noemen:

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 17 januari 1951 te Terborg. De eerste vier jaar van de middelbare school bracht hij door te 's Heerenberg op het klein-seminarie van de Salesianen van Don Bosco, de laatste twee jaar (Gymnasium β) op het Katholiek Gelders Lyceum te Arnhem, waar hij in 1969 het eind-diploma behaalde. In hetzelfde jaar begon hij met de studie in de geneeskunde aan de Katholieke Universiteit te Nijmegen. Vanaf zijn tweede studiejaar was hij part-time in dienst van de regionale ambulancedienst "Maas en Waal" te Druten. Het kandidaatsexamen werd behaald in 1973. Gedurende de doctoraalfase was hij student-assistent op de afdelingen orthopedie, traumatologie en anatomie. Op laatstgenoemde afdeling was hij enkele jaren betrokken bij het practicum-onderwijs en verrichtte hij o.l.v. Prof. Dr. A.H.M. Lohman onderzoek naar het olfactoire systeem bij de Tupinambis nigropunctatis. Na het doctoraalexamen in januari 1977 kwam hij als wetenschappelijk assistent in dienst van de afdeling Anatomie en Embryologie (hoofd: Prof. Dr. H.J. Lammers), alwaar dit promotie-onderzoek gestart werd, aanvankelijk onder leiding van Dr. I.M. Valk (fysische anthropologie) en later onder leiding van Dr. A.G.H. Smals (endocrinologie). Na het behalen van het artsexamen in februari 1980 werd het dienstverband voortgezet als wetenschappelijk medewerker in tijdelijke dienst tot 1 november 1981. Op 1 december zal hij beginnen met de opleiding tot huisarts.

STELLINGEN

I

De techniek en methode van ulnalengtemeting zoals ontwikkeld door Valk maakt het mogelijk op zeer korte termijn het effect van hormonale therapie bij individuele patiënten met groeistoornissen te meten.

Dit proefschrift.

II

Het gevonden dagritme in de ulnalengte bij gelijktijdig optredende groei suggereert, dat deze groei 's nachts plaats vindt.

Dit proefschrift.

III

Bij het voorschrijven van de "combinatiepil" aan jonge meisjes dient rekening te worden gehouden met het groeiremmende effect van lage doses oestrogenen.

Dit proefschrift.

J.J. v.d. Werff ten Bosch & A. Bot (1981), Ned J Med 24, 52.

IV

Het alkalische fosfatase in het serum van gezonde opgroeiende kinderen is een goede maat voor de groeiactiviteit.

Dit proefschrift.

Round et al. (1979), Ann Hum Biol 6, 129.

V

Het onderzoek naar de groeiversnelling na ziekte - met name na koorts - werd reeds in 1877 door Bowditch aanbevolen.

H.P. Bowditch (1877) Growth of Children, Boston.

VI

Om de invloed van het seizoen op de lengtegroei van kinderen te verklaren dient o.a. de invloed van meteorologische factoren op dit groeiproces te worden bestudeerd.

VII

Het feit, dat de moderne geneeskunde zeer doeltreffend is bij de behandeling van specifieke symptomen, wil nog niet zeggen, dat ze de gezondheid van de patiënt beter is gaan dienen.

Ivan Illich (1978) Grenzen aan de Geneeskunde.

VIII

De zogenaamde kleine co-schappen KNO, dermatologie en oogheelkunde dienen zeker voor a.s. huisartsen drastisch te worden uitgebreid, waarbij het zelf werken een grotere plaats zou moeten innemen.

IX

Het anatomie-onderwijs op de medische faculteit zou met behoud van vorm en inhoud d.m.v. accentverschuivingen meer afgestemd moeten worden op de kliniek. Daarvoor is een intensiever contact tussen anatomen en klinici noodzakelijk.

X

Een groot aantal jonge huisartsen zal vanwege de hoge schuldenlast noodgedwongen nieuwe ontwikkelingen in de eerstelijns zorg tegenhouden.

Stellingen behorende bij het proefschrift van J.S.G. van den Bosch "Short term growth in tall and short statured adolescents treated with sex hormones", Nijmegen, 27 november 1981.