

## EFFECT OF GROWTH HORMONE TREATMENT ON THE ADULT HEIGHT OF CHILDREN WITH CHRONIC RENAL FAILURE

DIETER HAFFNER, M.D., FRANZ SCHAEFER, M.D., RICHARD NISSEL, M.D., ELKE WÜHL, M.D., BURKHARD TÖNSHOFF, M.D., AND OTTO MEHLS, M.D., FOR THE GERMAN STUDY GROUP FOR GROWTH HORMONE TREATMENT IN CHRONIC RENAL FAILURE\*

**ABSTRACT**

**Background** Growth hormone treatment stimulates growth in short children with chronic renal failure. However, the extent to which this therapy increases final adult height is not known.

**Methods** We followed 38 initially prepubertal children with chronic renal failure treated with growth hormone for a mean of 5.3 years until they reached their final adult height. The mean ( $\pm$ SD) age at the start of treatment was  $10.4 \pm 2.2$  years, the mean bone age was  $7.1 \pm 2.3$  years, and the mean height was  $3.1 \pm 1.2$  SD below normal. Fifty matched children with chronic renal failure who were not treated with growth hormone served as controls.

**Results** The children treated with growth hormone had sustained catch-up growth, whereas the control children had progressive growth failure. The mean final height of the growth hormone-treated children was 165 cm for boys and 156 cm for girls. The mean final adult height of the growth hormone-treated children was  $1.6 \pm 1.2$  SD below normal, which was 1.4 SD above their standardized height at base line ( $P < 0.001$ ). In contrast, the final height of the untreated children ( $2.1 \pm 1.2$  SD below normal) was 0.6 SD below their standardized height at base line ( $P < 0.001$ ). Although prepubertal bone maturation was accelerated in growth hormone-treated children, treatment was not associated with a shortening of the pubertal growth spurt. The total height gain was positively associated with the initial target-height deficit and the duration of growth hormone therapy and was negatively associated with the percentage of the observation period spent receiving dialysis treatment.

**Conclusions** Long-term growth hormone treatment of children with chronic renal failure induces persistent catch-up growth, and the majority of patients achieve normal adult height. (N Engl J Med 2000; 343:923-30.)

©2000, Massachusetts Medical Society.

**C**HILDREN with chronic renal failure are at high risk for growth retardation and decreased adult height.<sup>1</sup> Therapy with recombinant human growth hormone increases the growth rate and improves the standardized height (height expressed as the number of standard deviations from normal height) in prepubertal children with chronic renal failure.<sup>2,3</sup> However, whether the final height is improved by this treatment is unknown. In children with growth hormone deficiency or idiopathic short stature, it has been suspected that growth

hormone accelerates the onset or progression of puberty, thereby neutralizing the effect of any treatment-induced acceleration of prepubertal growth on adult height.<sup>4,5</sup>

The factors that influence growth and the use of growth hormone therapy in children with chronic renal failure vary, depending on the type of treatment they are receiving for their renal disease. Whereas growth before and during dialysis treatment is affected by nutritional, metabolic, and endocrine alterations, growth after renal transplantation is affected by glucocorticoid and other immunosuppressive therapy and graft failure.<sup>1</sup> Among children treated with growth hormone, treatment is usually discontinued after transplantation, but it is sometimes reinstated if the growth rate remains low. This results in large variations in the duration of growth hormone treatment, making assessment of its long-term efficacy difficult.

We determined the final adult height of 38 children with chronic renal failure who were treated with growth hormone for up to nearly nine years. The results were compared with those for a group of 50 similar children who did not receive growth hormone therapy because their growth retardation at the beginning of the study was less marked than that of the treated children.

**METHODS****Study Subjects**

The subjects were participants in a German multicenter study<sup>3,6</sup> of children with chronic renal failure who had a standard-deviation score for height of  $-2.0$  or below (denoting a height 2.0 SD or more below normal) or a height velocity below the 25th percentile during the year before the beginning of treatment; they had a glomerular filtration rate of less than 60 ml per minute per  $1.73 \text{ m}^2$  of body-surface area for children treated conservatively (i.e., without dialysis) or more than 20 ml per minute per  $1.73 \text{ m}^2$  for those who had received a renal allograft. The study protocol was approved by the ethics committee of Heidelberg University and the local ethics committee of each participating center. Written informed consent was obtained from the parents and oral or written consent from the children.

Between 1987 and 1994, 142 children were enrolled in the trial. The children were treated for at least one year with growth hormone and remained prepubertal (defined as Tanner stage 1) for at least the first year of treatment. One hundred four children had not yet reached their final adult height, as defined by a height ve-

From the Division of Pediatric Nephrology, University Children's Hospital, Heidelberg, Germany. Address reprint requests to Dr. Mehls at the Division of Pediatric Nephrology, University Children's Hospital, Im Neuenheimer Feld 150, D-69120 Heidelberg, Germany, or at otto\_mehls@med.uni-heidelberg.de.

\*Other investigators are listed in the Appendix.

locity below 1 cm per year or by evidence of epiphyseal closure on radiography of the hand, by April 1999. The analysis presented here is restricted to the 38 children (32 boys and 6 girls) who had reached their final adult height by that date (Table 1). Their mean ( $\pm$ SD) age at the start of treatment was  $10.4\pm 2.2$  years, their bone age was  $7.1\pm 2.3$  years, and their mean standard-deviation score for height was  $-3.1\pm 1.2$ . Twenty-three of these 38 children had obstructive or refluxive uropathy, renal dysplasia, or renal hypoplasia; 7 had congenital or hereditary nephropathy; 6 had glomerular disease; and 2 had other renal diseases. At the start of growth hormone therapy, 24 children were receiving conservative treatment, 5 were undergoing dialysis (continuous peritoneal dialysis in 2 and hemodialysis in 3), and 9 had functioning renal allografts. During the study period, 11 children who had initially received conservative treatment were switched to dialysis, and 9 of these children subsequently received renal allografts. The duration of each type of treatment (medical therapy, dialysis, and time with a renal transplant) was calculated as the percentage of the total observation period for each patient. The mean values are given in Table 2.

Each child received a daily subcutaneous injection of growth hormone (Genotropin, Pharmacia & Upjohn) in the evening, for a total weekly dose of 1 IU (0.33 mg) per kilogram of body weight. The 11 children who were switched from conservative treatment to dialysis during the study continued to receive growth hormone. Treatment was discontinued before the attainment of final adult height in 14 children. Nine of the 14 received renal allografts, and 5 wished to discontinue treatment, including 3 who reached their genetic target height before epiphyseal closure. The follow-up of these children continued until they reached their final adult height. The median follow-up from first observation to final adult height was 7.6 years (range, 5.0 to 10.7). The median duration of growth hormone therapy was 5.3 years (range, 2.8 to 8.8).

### Control Group

Fifty children (31 boys and 19 girls) with chronic renal failure who had been regularly seen at Heidelberg University Children's

Hospital between 1984 and 1998 served as controls (Table 1). They were matched with the growth hormone-treated children with respect to age at first observation, underlying renal disease, treatment during the observation period, mean residual renal function or renal-allograft function, and cumulative dose of glucocorticoids (Table 2). They were not treated with growth hormone because they had relatively little or no growth retardation at base line, declined participation in the trial, or were ineligible for growth hormone therapy because of advanced puberty. Twenty-six of these 50 children had obstructive or refluxive uropathy, renal dysplasia, or renal hypoplasia; 4 had congenital or hereditary nephropathy; 14 had glomerular disease; and 6 had other renal diseases. All of these children were prepubertal at base line and were followed until they achieved their final adult height. The median observation period was 8.3 years (range, 5.2 to 10.1). At base line, 49 children were receiving conservative treatment and 1 was undergoing hemodialysis. During the observation period, 38 children who initially received conservative treatment were switched to dialysis, and 35 subsequently received renal allografts.

### Clinical Studies

In the growth hormone-treated and control children, standard anthropometric measurements were obtained at three-to-six-month intervals. Radiographs of the hand were obtained at approximately 12-month intervals. Bone age was determined by the Tanner-Whitehouse-2 method.<sup>7</sup> Reference data were taken from the Zurich Longitudinal Growth Study.<sup>8</sup> The genetic target height was calculated as the midparental height (the mean of the two parents' heights) plus 10 cm for boys and minus 2.6 cm for girls.<sup>9</sup> The predicted adult height was calculated by the Tanner method.<sup>7</sup> The glomerular filtration rate was estimated from the calculated creatinine clearance.<sup>10</sup>

### Statistical Analysis

To minimize the influence of measurement errors, the height data were smoothed by kernel estimation, a mathematical process

**TABLE 1. ANTHROPOMETRIC CHARACTERISTICS OF GROWTH HORMONE-TREATED AND CONTROL CHILDREN WITH CHRONIC RENAL FAILURE.**

CHARACTERISTIC	Boys			Girls		
	TREATED (N=32)	CONTROL (N=31)	P VALUE*	TREATED (N=6)	CONTROL (N=19)	P VALUE*
	mean $\pm$ SD			mean $\pm$ SD		
Age at base line (yr)	10.6 $\pm$ 2.3	10.0 $\pm$ 1.2	0.20	9.9 $\pm$ 3.0	9.4 $\pm$ 2.3	0.67
Bone age at base line (yr)	6.9 $\pm$ 2.4	9.0 $\pm$ 1.7	<0.001	7.8 $\pm$ 2.5	8.5 $\pm$ 2.4	0.58
Height at base line (cm)	123.0 $\pm$ 13.3	131.2 $\pm$ 11.0	0.012	124.3 $\pm$ 18.2	126.5 $\pm$ 13.5	0.75
Height at base line (standard-deviation score)	-3.2 $\pm$ 1.3	-1.4 $\pm$ 1.3	<0.001	-2.5 $\pm$ 1.0	-1.6 $\pm$ 1.3	0.023
Genetic target height (cm)	175.3 $\pm$ 4.8	177.9 $\pm$ 7.9	0.12	168.3 $\pm$ 7.8	168.0 $\pm$ 5.3	0.92
Predicted adult height at base line (cm)	163.4 $\pm$ 10.6	170.1 $\pm$ 9.6	0.011	155.8 $\pm$ 7.5	163.3 $\pm$ 5.6	0.015
Duration of growth hormone treatment (yr)	5.4 $\pm$ 1.6	—	<0.001	5.0 $\pm$ 2.2	—	<0.001
Age at start of pubertal growth spurt (yr)†	13.6 $\pm$ 1.5	13.0 $\pm$ 1.7	0.022	12.1 $\pm$ 1.9	12.0 $\pm$ 1.8	0.91
Duration of pubertal growth spurt (yr)‡	4.6 $\pm$ 1.9	5.2 $\pm$ 1.2	0.14	4.1 $\pm$ 1.5	4.6 $\pm$ 1.1	0.38
Total prepubertal height gain (cm)§	18.6 $\pm$ 9.3	9.9 $\pm$ 4.8	<0.001	16.6 $\pm$ 8.7	9.1 $\pm$ 9.8	0.014
Total pubertal height gain (cm)¶	23.5 $\pm$ 7.0	21.0 $\pm$ 6.7	0.15	15.1 $\pm$ 6.3	16.3 $\pm$ 7.0	0.71
Final adult height (cm)	165.2 $\pm$ 8.2	162.1 $\pm$ 9.0	0.021	156.2 $\pm$ 9.8	151.9 $\pm$ 6.7	0.028
Final adult height (standard-deviation score)	-1.7 $\pm$ 1.2	-2.1 $\pm$ 1.3	0.013	-1.3 $\pm$ 1.6	-2.1 $\pm$ 1.2	0.02

\*P values are for comparisons between growth hormone-treated and control children of the same sex.

†Normal values are 10.9 $\pm$ 1.0 years for boys and 9.6 $\pm$ 1.0 years for girls.

‡Normal values are 6.5 $\pm$ 1.0 years for boys and 5.9 $\pm$ 1.0 years for girls.

§Gain was measured from the first observation.

¶Normal values are 32.7 $\pm$ 7.2 cm for boys and 28.7 $\pm$ 10.0 cm for girls.

ture that applies moving weighted averages to raw data.<sup>11,12</sup> From the smoothed growth curve, the corresponding height-velocity curve was calculated as the first derivative of height by time. The point at which the height-velocity curve reached a first maximum after the start of growth hormone treatment was defined as the growth hormone–induced peak height velocity. The time of maximal height velocity during puberty defined the pubertal peak height velocity, and the preceding nadir defined the minimal prespurt height velocity (the starting point of the pubertal growth spurt).<sup>11</sup> The end of the pubertal growth spurt was defined as the age at which the height-velocity curve permanently dropped below 1 cm per year.

In order to obtain a synchronized mean growth curve, the individual smoothed growth curves were synchronized according to the following points in time: the time at the start of growth hormone treatment or, in the control group, the time of first observation; the peak height velocity in the growth hormone–treated patients; the minimal prespurt height velocity; the pubertal peak height velocity; and the time of the end of the pubertal growth spurt.<sup>13</sup> For this purpose, a synchronization program was applied that transforms the time scale of each individual curve to align the characteristic points with their respective means.<sup>14</sup>

The results are expressed as means  $\pm$  SD. Comparisons between groups were performed by analysis of variance, followed by Duncan's multiple-range test. Longitudinal changes in the anthropometric measurements were evaluated by repeated-measures analysis of variance, including a within-subject factor (time) and a between-subject factor (growth hormone–treated vs. control children). Pairwise comparisons between different time points were performed with the Contrast option of the general-linear-model procedure in SAS/STAT software.

Univariate linear regression analysis was performed to identify possible predictors of the total increase in height during growth hormone treatment and for the prepubertal and pubertal growth periods separately. The following variables were examined: age; bone age; degree of bone-age retardation; standard-deviation score for the height; genetic-target-height deficit (the standard-deviation score for the height minus the standard-deviation score for the genetic target height) at base line; duration of growth hormone treatment; percentage of time during which children were receiving conservative treatment, were undergoing dialysis, or had undergone transplantation; glomerular filtration rate; sex; age at start of the pubertal growth spurt; duration of the pubertal growth spurt; and

cumulative glucocorticoid dose in patients who received renal allografts. Multiple regression analysis was performed by starting with a model that included all potential predictors, with stepwise elimination of variables that did not contribute significantly to the overall variance of the model. All P values are two-sided.

## RESULTS

### Prepubertal Growth

The synchronized mean height-velocity curves for the growth hormone–treated and control children, as well as for a reference population of normal children, are shown in Figure 1. During the prepubertal observation period, the height velocity in the growth hormone–treated children increased over base line and exceeded the values in both the control and the normal children ( $P < 0.001$  for both comparisons). The mean height velocity in the growth hormone–treated children increased from 3.3 cm per year in boys and 3.7 cm per year in girls to a maximum of 8.4 and 9.7 cm per year, respectively ( $P < 0.001$  for both comparisons). After this prepubertal peak, the height velocity decreased continuously until the start of the pubertal growth spurt. The mean minimal height velocity before the start of the pubertal growth spurt was higher in the growth hormone–treated children than in the control children ( $P < 0.001$ ) and was similar to that in the normal children. The total height gain during the prepubertal observation period was approximately twice as great in the growth hormone–treated children as in the control children (Table 1).

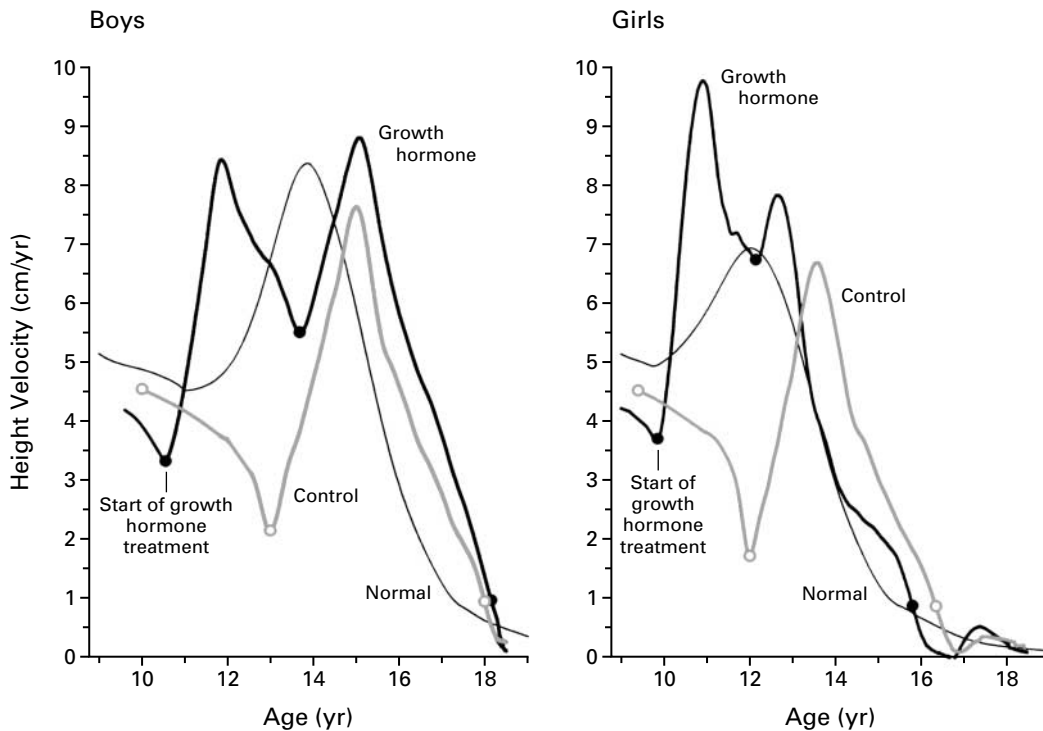
### Pubertal Growth

The mean peak height velocity during the pubertal growth spurt was not significantly higher in the growth hormone–treated children (8.8 cm per year for boys and 7.8 cm per year for girls) than in the

**TABLE 2.** TREATMENT FOR CHRONIC RENAL FAILURE AND CHANGE IN GLOMERULAR FILTRATION RATE DURING THE OBSERVATION PERIOD IN GROWTH HORMONE–TREATED AND CONTROL CHILDREN.\*

VARIABLE	TREATED CHILDREN (N=38)	CONTROLS (N=50)	P VALUE
Treatment (% of observation period)			
Conservative	47	53	0.48
Dialysis	24	20	0.61
Transplantation	29	27	0.88
Glomerular filtration rate during observation period (ml/min/1.73 m <sup>2</sup> )			
Conservative treatment	25 $\pm$ 17	33 $\pm$ 27	0.20
Post-transplantation	62 $\pm$ 17	65 $\pm$ 25	0.66
Yearly decrease in glomerular filtration rate during observation period (ml/min/1.73 m <sup>2</sup> )			
Conservative treatment	1.6 $\pm$ 3.0	2.3 $\pm$ 3.8	0.44
Post-transplantation	3.9 $\pm$ 6.3	4.6 $\pm$ 8.2	0.76
Cumulative dose of methylprednisolone (g/m <sup>2</sup> )	3.3 $\pm$ 0.6	3.1 $\pm$ 0.7	0.33

\*Plus-minus values are means  $\pm$  SD.



**Figure 1.** Synchronized Mean Height-Velocity Curves during Growth Hormone Treatment for 38 Children (32 Boys and 6 Girls) with Chronic Renal Failure, as Compared with 50 Control Children with Chronic Renal Failure Not Treated with Growth Hormone and 232 Normal Children, According to Sex.

The circles indicate the time of the first observation (the start of growth hormone treatment in the treated children), the time of minimal prespurt height velocity, and the end of the pubertal growth spurt.

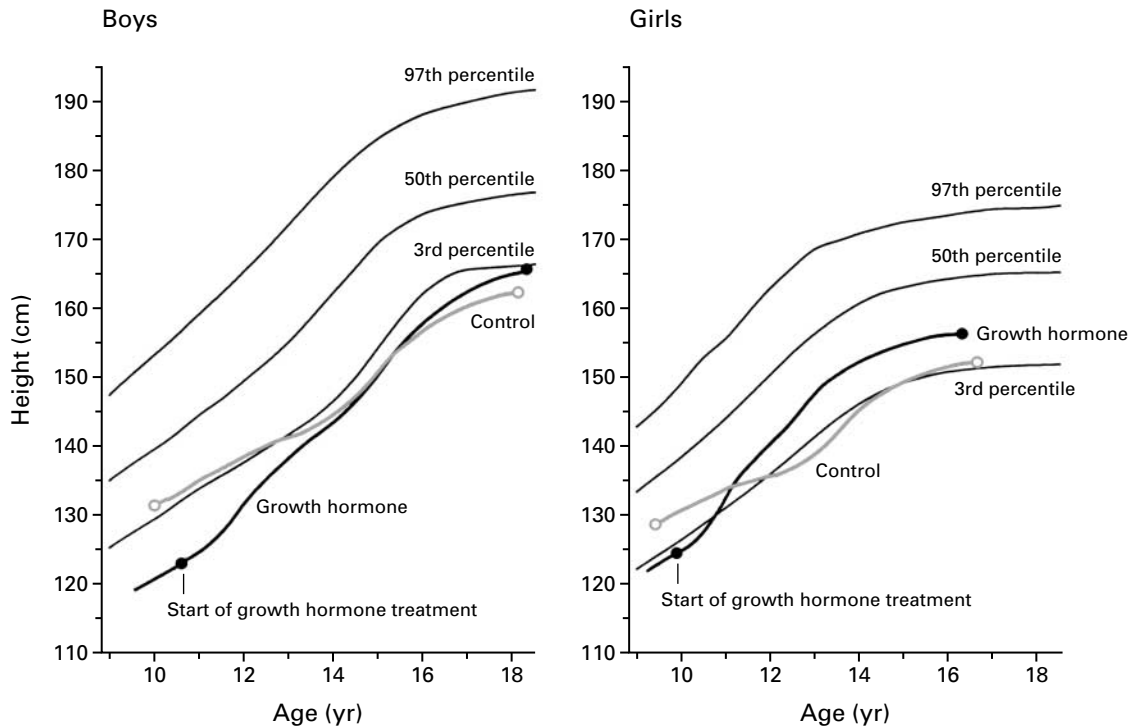
control children (7.6 cm per year for boys,  $P=0.26$ ; 6.7 cm per year for girls,  $P=0.18$ ) or the normal children (7.8 cm per year for boys,  $P=0.53$ ; 6.5 cm per year for girls,  $P=0.27$ ). The onset of the pubertal growth spurt was delayed in the children with chronic renal failure by approximately 2.5 years, and the duration of the growth spurt was 1.6 years shorter than in the normal children ( $P<0.001$  for the comparisons of normal children with growth hormone-treated children and control children). In boys, but not in girls, the onset of the pubertal growth spurt was more delayed in the growth hormone-treated children than in the control children (Table 1). The duration of the pubertal growth spurt was not shorter in the growth hormone-treated children. The total pubertal height gain was similar in the growth hormone-treated children and the control children and was 65 percent of that in the normal children because of the shorter pubertal growth spurt (Fig. 1).

#### Final Adult Height

The growth hormone-induced stimulation of height velocity resulted in sustained catch-up growth

in the treated children, whereas the control children had progressive growth failure (Fig. 2). In the treated children, the standardized height increased from base line by a mean of 1.4 SD (1.5 for boys and 1.2 for girls) to a mean final adult height  $1.6\pm 1.2$  SD below normal (1.7 for boys and 1.3 for girls,  $P<0.001$  for both comparisons) (Table 1). In contrast, the standardized height of the control children decreased from base line by a mean of 0.6 SD (0.7 for boys and 0.5 for girls) to a mean final adult height  $2.1\pm 1.2$  SD below normal (2.1 for both boys and girls,  $P<0.001$  for both comparisons) (Table 1).

The growth hormone-treated children reached their final adult height at a mean age of 18.2 years for boys and 16.2 years for girls (Table 1) and a bone age of 15.9 years for boys and 14.7 years for girls. Sixty-five percent of these children reached an adult height within the normal range (within 2 SD of normal height). However, the mean final adult height was below the genetic target height by 10.1 cm in boys ( $P=0.005$ ) and 12.1 cm in girls ( $P=0.007$ ). The control children reached their final adult height at a mean chronologic age of 18.1 years for boys and



**Figure 2.** Synchronized Mean Growth Curves during Growth Hormone Treatment for 38 Children (32 Boys and 6 Girls) with Chronic Renal Failure, as Compared with 50 Control Children with Chronic Renal Failure Not Treated with Growth Hormone, According to Sex.

Normal values are indicated by the 3rd, 50th, and 97th percentiles. The circles indicate the time of the first observation (the start of growth hormone treatment in the treated children) and the end of the pubertal growth spurt.

16.6 years for girls and a mean bone age of 15.6 years for boys and 14.9 years for girls. These values were lower than those in the growth hormone-treated children and markedly lower than the genetic target heights (15.8 cm lower in boys and 16.1 cm lower in girls,  $P < 0.001$  for both comparisons).

#### Bone Maturation and Change in Predicted Adult Height

During the prepubertal observation period, the bone age increased faster in the growth hormone-treated boys ( $1.1 \pm 0.3$  years per calendar year) and girls ( $1.2 \pm 0.2$  years per calendar year) than in the control children ( $0.8 \pm 0.2$  year per calendar year for boys,  $P = 0.004$ ;  $0.7 \pm 0.4$  year per calendar year for girls,  $P = 0.007$ ). Bone maturation during puberty was accelerated in the growth hormone-treated boys as compared with the control boys ( $1.2 \pm 0.3$  vs.  $0.9 \pm 0.2$  year per calendar year,  $P = 0.008$ ), but not in the growth hormone-treated girls ( $1.0 \pm 0.3$  vs.  $1.0 \pm 0.2$  year per calendar year,  $P = 0.67$ ).

Growth hormone treatment significantly increased the predicted adult height in boys during the prepubertal observation period (Fig. 3). However, the final adult height was only slightly (1.8 cm) higher than the predicted adult height at base line ( $P = 0.10$ ). In

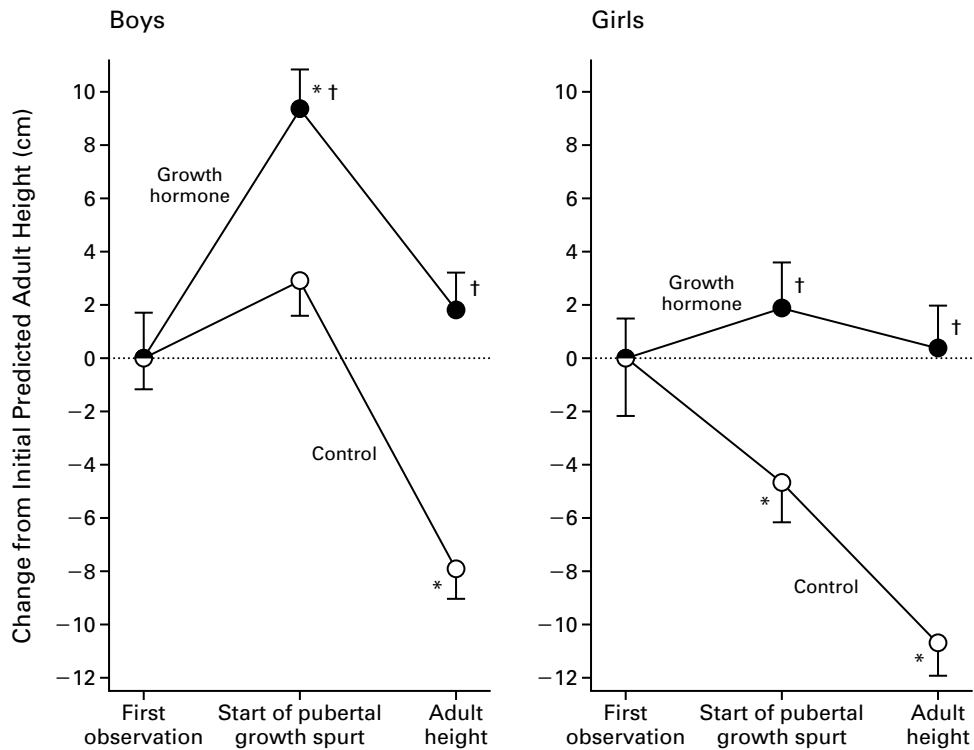
the growth hormone-treated girls, the predicted adult height did not change significantly. In the control children, the adult height was overestimated at first observation by 10.3 cm (8.0 cm in boys and 11.4 cm in girls,  $P < 0.001$  for both comparisons).

#### Predictors of Growth

Multiple regression analysis revealed that the absolute as well as the standardized height gain during the observation period was significantly associated with a longer duration of the prepubertal and pubertal observation periods, a longer duration of growth hormone therapy, a greater initial target-height deficit, a lower percentage of time spent on dialysis, and male sex; these factors together explained 61 to 87 percent of the overall variability (Table 3). The pubertal height gain in the growth hormone-treated children was positively correlated with the duration of treatment during the pubertal growth period ( $P < 0.001$ ).

#### DISCUSSION

This study provides evidence that growth hormone treatment results in sustained catch-up growth and a final height within the normal range in the major-



**Figure 3.** Change from Initially Predicted Adult Height at Base Line in 38 Children (32 Boys and 6 Girls) with Chronic Renal Failure Who Received Growth Hormone Treatment, as Compared with 50 Control Children with Chronic Renal Failure Who Did Not Receive Growth Hormone, According to Sex.

Values are means  $\pm$ SD. Asterisks indicate significant differences from the previous period ( $P < 0.001$ ), and daggers significant differences from the children who were not treated with growth hormone ( $P < 0.001$ ).

**TABLE 3.** PREDICTORS OF GROWTH DURING THE OBSERVATION PERIOD IN THE GROWTH HORMONE-TREATED AND CONTROL CHILDREN COMBINED.

PERIOD AND PREDICTOR	EFFECT	PARTIAL R <sup>2</sup>	CUMULATIVE R <sup>2</sup>	P VALUE
Prepubertal period (change in cm of height)				
Increased duration of prepubertal period	Positive	0.67	0.87	<0.001
Increased duration of growth hormone therapy	Positive	0.13		<0.001
Greater initial target-height deficit	Positive	0.04		<0.001
Greater % of time spent on dialysis	Negative	0.03		0.006
Pubertal growth period (change in cm of height)				
Increased duration of pubertal period	Positive	0.45	0.61	<0.001
Increased duration of growth hormone therapy	Positive	0.11		<0.001
Male sex	Positive	0.05		0.005
Total observation period (change in cm of height)				
Greater initial target-height deficit	Positive	0.68	0.78	<0.001
Increased duration of growth hormone therapy	Positive	0.06		0.002
Greater % of time spent on dialysis	Negative	0.04		0.004
Total observation period (change in standard-deviation score)				
Increased duration of growth hormone therapy	Positive	0.58	0.64	<0.001
Greater initial target-height deficit	Positive	0.06		0.008

ity of children with growth failure due to chronic renal failure. The beneficial effect of long-term growth hormone therapy was even more impressive when the natural history of growth in the control group, made up of children with similar medical characteristics but less initial growth retardation, was considered. In these children, the final adult height was 10.3 cm below the initially predicted adult height, whereas in the growth hormone-treated children, the final adult height exceeded the predicted adult height only slightly. The growth-hormone-treated children were only slightly taller than the control children at their final adult height (3 cm for boys and 4 cm for girls), but it is likely that the growth hormone-treated children would have had a much poorer outcome without treatment, since these children were already shorter than the controls at the time of initial observation.

A crucial methodologic issue in this study was the use of an appropriate control group. It was not considered justified to withhold growth hormone, the only growth-promoting treatment with well-established short-term efficacy in children with chronic renal failure, permanently from a large group of severely growth-retarded children. We therefore decided to collect growth data from children who matched the growth hormone-treated children with respect to relevant clinical characteristics but who were not treated with growth hormone because they had less marked initial growth retardation or because they declined to participate in the trial of growth hormone therapy.

It may be questioned whether similarly progressive growth failure would have developed in a control group of children whose initial growth retardation was similar to that in the growth hormone-treated children. However, the decrease in standardized height in the control group during follow-up is quantitatively similar to that found in several previous studies of spontaneous growth in children with chronic renal failure.<sup>13,15,16</sup> Moreover, the change over time in the standard-deviation score for height in the control group was not correlated with the initial standard-deviation score for height, a result suggesting that the factors affecting growth during chronic renal failure and after renal transplantation operate throughout childhood and may compromise growth irrespective of the degree of growth failure at a particular age.

In this study, the impressive increment in standardized height in response to growth hormone therapy during the prepubertal years persisted during puberty, although treatment was discontinued in some children who received renal transplants. In the past, there has been concern that the increments in growth rates and standard-deviation scores for height that are caused by growth hormone treatment during the prepubertal years might be offset by an earlier onset or shorter duration of pubertal growth.<sup>4,5</sup> So far, a decrease in the standard-deviation scores for height

during puberty has been noted in some, but not all, studies of children with idiopathic short stature or growth hormone deficiency.<sup>5,17-22</sup>

In our study, bone maturation during the prepubertal period accelerated slightly in the growth hormone-treated children, as compared with the control children. However, the growth hormone-induced prepubertal growth stimulation was sufficient to override the adverse effect of stimulated skeletal maturation, resulting in a marked increase in prepubertal height gain and predicted adult height at the onset of puberty. Skeletal maturation during puberty was further increased in the growth hormone-treated boys, but not in the girls, in keeping with previous observations in boys with idiopathic short stature.<sup>5,18,19</sup> The pubertal growth period was significantly shorter in the children with chronic renal failure, regardless of growth hormone treatment. The markedly diminished pubertal height gain in children with chronic renal failure before and after renal transplantation has been noted previously<sup>13,23</sup> and is believed to be due to an altered interaction between cartilage growth and differentiation under the influence of endogenous sex steroids and, in renal-transplant recipients, exogenous glucocorticoids.<sup>24</sup>

The total height gain during the observation period in the growth hormone-treated children was positively associated with the initial degree of growth retardation. This phenomenon has also been observed in children with idiopathic short stature or Turner's syndrome who were treated with growth hormone,<sup>18,25</sup> suggesting that the efficacy of growth hormone depends on the biologic "demand" for catch-up growth.

Another major factor affecting growth in children with chronic renal failure is the treatment they receive. As in earlier studies,<sup>26</sup> the growth response was poorest in children undergoing long-term dialysis. This finding is compatible with the notion that growth hormone resistance in children with chronic renal failure is only partially overcome by exogenous growth hormone. Thus, the availability of growth hormone does not eliminate the necessity to minimize the time spent on dialysis in order to optimize growth.

In conclusion, the beneficial effect of growth hormone in children with chronic renal failure is preserved during puberty and results in an increase in final adult height.

Supported by Pharmacia & Upjohn, Stockholm, Sweden.

*We are indebted to Professor Theo Gasser (Technische Eidgenössische Hochschule, Zurich, Switzerland) and Dr. Eva Herrmann (Technische Universität, Darmstadt, Germany) for introducing us to the auxologic tools used in the study, and to Dr. Reinhard Feneberg for developing a computer program to facilitate the use of the smoothing and synchronization procedures.*

#### APPENDIX

The other members of the German Study Group for Growth Hormone Treatment in Chronic Renal Failure who contributed data to this study are

as follows (in alphabetical order of the cities): K. Rager (Bad Mergentheim); G. Filler and J. Gellermann (Berlin); R. Mallmann (Bonn); U. Querfeld (Cologne); K.E. Bonzel and B. Weiß (Essen); J. Dippell (Frankfurt); L.B. Zimmerhackl (Freiburg); D.E. Müller-Wiefel (Hamburg); G. Offner and N. Albers (Hannover); J. Misselwitz and G. Rönnefarth (Jena); H. Eichstädt, C. Greiner, and E. Keller (Leipzig); D. Sasse and M. Sörgel (Marburg); E. Kuwertz-Bröking (Münster); B. Klare and C.R. Montoya (Munich); and M. Mix and M. Wigger (Rostock).

## REFERENCES

1. Schaefer F, Mehls O. Endocrine and growth disturbances. In: Barratt TM, Avner ED, Harmon WE, eds. *Pediatric nephrology*. 4th ed. Baltimore: Lippincott Williams & Wilkins, 1999:1197-230.
2. Fine RN, Kohaut E, Brown D, Kuntze J, Attie KM. Long-term treatment of growth retarded children with chronic renal insufficiency, with recombinant human growth hormone. *Kidney Int* 1996;49:781-5.
3. Haffner D, Wühl E, Schaefer F, et al. Factors predictive of the short- and long-term efficacy of growth hormone treatment in prepubertal children with chronic renal failure. *J Am Soc Nephrol* 1998;9:1899-907.
4. Darendeliler F, Hindmarsh PC, Preece MA, Cox L, Brook CGD. Growth hormone increases rate of pubertal maturation. *Acta Endocrinol (Copenh)* 1990;122:414-6.
5. Kawai M, Momoi T, Yorifuji T, Yamanaka C, Sasaki H, Furusho K. Unfavorable effects of growth hormone therapy on the final height of boys with short stature not caused by growth hormone deficiency. *J Pediatr* 1997;130:205-9.
6. Tönshoff B, Haffner D, Mehls O, et al. Efficacy and safety of growth hormone treatment in short children with renal allografts: three year experience. *Kidney Int* 1993;44:199-207.
7. Tanner JM, Marshall WA, Healy MJ, Goldstein H. Assessment of skeletal maturity and prediction of adult height (TW2 method). 2nd ed. New York: Academic Press, 1983.
8. Prader A, Largo RH, Molinari L, Issler C. Physical growth of Swiss children from birth to 20 years of age: first Zurich longitudinal study of growth and development. *Helv Paediatr Acta Suppl* 1989;52:1-125.
9. Molinari L, Largo RH, Prader A. Target height and secular trend in the Swiss population. In: Borms J, ed. *Human growth and development*. New York: Plenum Press, 1985:193-200.
10. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am* 1987;34:571-90.
11. Gasser T, Köhler W, Müller HG, et al. Velocity and acceleration of height growth using kernel estimation. *Ann Hum Biol* 1984;11:397-411.
12. Gasser T, Kneip A, Ziegler P, Largo R, Prader A. A method for determining the dynamics and intensity of average growth. *Ann Hum Biol* 1990;17:459-74.
13. Schaefer F, Seidel C, Binding A, et al. Pubertal growth in chronic renal failure. *Pediatr Res* 1990;28:5-10.
14. Gasser T. Analysing curves using kernel estimators. *Pediatr Nephrol* 1991;5:447-50.
15. Hokken-Koelega AC, van Zaal MA, van Bergen W, et al. Final height and its predictive factors after renal transplantation in childhood. *Pediatr Res* 1994;36:323-8.
16. Tejani A, Cortes L, Sullivan EK. A longitudinal study of the natural history of growth post-transplantation. *Kidney Int Suppl* 1996;53:103-8.
17. Hochberg Z, Leiberman E, Landau H, Koren R, Zadik Z. Age as a determinant of the impact of growth hormone therapy on predicted adult height. *Clin Endocrinol (Oxf)* 1994;41:331-5.
18. Locher S, Cambiaso P, Setzu S, et al. Final height after growth hormone therapy in non-growth-hormone-deficient children with short stature. *J Pediatr* 1994;125:196-200.
19. Hindmarsh PC, Brook CGD. Final height of short normal children treated with growth hormone. *Lancet* 1996;348:13-6.
20. August GP, Julius JR, Blethen SL. Adult height in children with growth hormone deficiency who are treated with biosynthetic growth hormone: the National Cooperative Growth Study experience. *Pediatrics* 1998;102:512-6.
21. McCaughey ES, Mulligan J, Voss LD, Betts PR. Randomised trial of growth hormone in short normal girls. *Lancet* 1998;351:940-4.
22. Hintz RL, Attie KM, Baptista J, Roche A. Effect of growth hormone treatment on adult height of children with idiopathic short stature. *N Engl J Med* 1999;340:502-7.
23. van Diemen-Steenvoorde R, Donckerwolcke RA, Brackel H, Wolff ED, de Jong MCJW. Growth and sexual maturation in children after kidney transplantation. *J Pediatr* 1987;110:351-6.
24. Schaefer F, Schärer K, Mehls O. Pathogenic mechanisms of pubertal growth failure in chronic renal failure. *Acta Paediatr Scand Suppl* 1991; 379:3-10.
25. Donaldson MDC. Growth hormone therapy in Turner syndrome — current uncertainties and future strategies. *Horm Res* 1997;48:Suppl 5:35-44.
26. Wühl E, Haffner D, Nissel R, Schaefer F, Mehls O, German Study Group for Growth Hormone Treatment in Chronic Renal Failure. Short dialyzed children respond less to growth hormone than patients prior to dialysis. *Pediatr Nephrol* 1996;10:294-8.

---

RECEIVE THE *JOURNAL'S* TABLE OF CONTENTS  
EACH WEEK BY E-MAIL

---

To receive the table of contents of the  
*New England Journal of Medicine* by e-mail  
every Wednesday evening,  
you can sign up through our Web site at:  
<http://www.nejm.org>

---