

EFFECT OF GROWTH HORMONE TREATMENT ON ADULT HEIGHT OF CHILDREN WITH IDIOPATHIC SHORT STATURE

RAYMOND L. HINTZ, M.D., KENNETH M. ATTIE, M.D., JOYCE BAPTISTA, PH.D.,
AND ALEX ROCHE, PH.D., FOR THE GENENTECH COLLABORATIVE GROUP*

ABSTRACT

Background Short-term administration of growth hormone to children with idiopathic short stature results in increases in growth rate and standard-deviation scores for height. However, the effect of long-term growth hormone therapy on adult height in these children is unknown.

Methods We studied 121 children with idiopathic short stature, all of whom had an initial height below the third percentile, low growth rates, and maximal stimulated serum concentrations of growth hormone of at least 10 μg per liter. The children were treated with growth hormone (0.3 mg per kilogram of body weight per week) for 2 to 10 years. Eighty of these children have reached adult height, with a bone age of at least 16 years in the boys and at least 14 years in the girls, and pubertal stage 4 or 5. The difference between the predicted adult height before treatment and achieved adult height was compared with the corresponding difference in three untreated normal or short-statured control groups.

Results In the 80 children who have reached adult height, growth hormone treatment increased the mean standard-deviation score for height (number of standard deviations from the mean height for chronologic age) from -2.7 to -1.4 . The mean (\pm SD) difference between predicted adult height before treatment and achieved adult height was $+5.0 \pm 5.1$ cm for boys and $+5.9 \pm 5.2$ cm for girls. The difference between predicted and achieved adult height among treated boys was 9.2 cm greater than the corresponding difference among untreated boys with initial standard-deviation scores of less than -2 , and the difference among treated girls was 5.7 cm greater than the difference among untreated girls.

Conclusions Long-term administration of growth hormone to children with idiopathic short stature can increase adult height to a level above the predicted adult height and above the adult height of untreated historical control children. (N Engl J Med 1999;340:502-7.)

©1999, Massachusetts Medical Society.

BEFORE biosynthetic growth hormone became available, sufficient growth hormone was available to treat only children with severe growth hormone deficiency. The presence of severe growth hormone deficiency was usually identified by a serum growth hormone response to provocative stimuli that was below an arbitrary value, frequently 10 μg per liter, or a low mean serum growth hormone concentration on frequent sam-

pling over a 12- or 24-hour period. These tests are expensive, have some risk,¹ depend on the presence or absence of sex steroids,² do not distinguish well between normal short children and those with growth hormone deficiency,³ and may give substantially different results in the same child at different times.^{4,5} Many children with short stature have peak stimulated serum growth hormone concentrations that are higher than the usual cutoff value for the diagnosis of growth hormone deficiency but have the same growth-retardation findings as children in whom growth hormone deficiency is diagnosed.

Several groups⁶⁻¹⁰ have treated children with short stature who did not have growth hormone deficiency according to classic criteria, commonly referred to as idiopathic short stature, and have obtained mixed results. In our previous studies, we found that such children had increases in growth rate, standard-deviation score for height, and predicted adult height after one and three years of growth hormone treatment.^{11,12} However, growth hormone treatment could have a short-term effect on growth but not increase adult height. In this report, we present the long-term results of our study, including data on adult height for 80 children treated with growth hormone for 2 to 10 years. The study was not placebo-controlled, and therefore we compared our results with the final heights of two groups of children from the Fels Longitudinal Study¹³ and 21 children with idiopathic short stature followed in our clinics who were not treated with growth hormone.

METHODS

Study Subjects

One hundred twenty-one children with short stature who did not meet the classic criteria for the diagnosis of growth hormone deficiency were enrolled in a multicenter study of growth hormone treatment sponsored by Genentech. Eighty-two percent of the children were white, 12 percent were Latino, and 6 percent were Asian, black, or members of other ethnic groups. The protocol was reviewed and approved by the human-subject research committees at all participating centers, and the parents of all children gave written informed consent for the study. When appropriate, the consent of the children was also obtained. All the children had base-line heights below the 3rd percentile (mean

From Stanford University, Stanford, Calif. (R.L.H.); Genentech, South San Francisco, Calif. (K.M.A., J.B.); and Wright State University, Yellow Springs, Ohio (A.R.). Address reprint requests to Dr. Hintz at the Department of Pediatrics, Rm. S-302, Stanford University Medical Center, Stanford, CA 94305.

*Other members of the Genentech Collaborative Group are listed in the Appendix.

standard-deviation score [number of standard deviations from the mean height for chronologic age], -2.7), growth rates that were less than the 50th percentile for age, and a peak stimulated serum growth hormone concentration of at least $10 \mu\text{g}$ per liter in response to at least two of the following stimuli: arginine, levodopa, clonidine, and insulin. All were prepubertal according to physical examination and had a bone age of less than 9 years (in girls) or less than 10 years (in boys), and none had any evidence of malnutrition or hormonal or systemic disease.

Clinical Studies and Follow-up

The children were evaluated at base line to determine height, weight, and Tanner pubertal stage, and they underwent a complete physical examination. A bone-age radiograph of the left hand and wrist was obtained; bone ages were determined at the Fels Institute by a radiologist who was unaware of the group assignments.¹⁴ Laboratory tests included measurements of serum growth hormone, insulin-like growth factor I, insulin-like growth factor-binding protein 3, and growth hormone-binding protein.

During the first year of participation in the study, each of the 121 children was randomly assigned to an observational control group or to a group receiving recombinant human growth hormone (total weekly dose, 0.3 mg per kilogram of body weight, with one third of the dose given subcutaneously three times weekly for one year). After the first year, all 121 children received 0.3 mg of growth hormone per kilogram per week, either daily or three times a week. During treatment, the children were seen every 3 months for measurement of height, and bone-age radiography and laboratory tests were repeated every 6 to 12 months. Growth hormone treatment was discontinued when the growth rate was less than 2 cm per year or when the parents and the children wished to discontinue treatment.

A total of 80 children (57 boys and 23 girls) completed between 2 and 10 years of growth hormone treatment and achieved adult height, as defined by a measured or projected bone age of at least 16 years for boys or 14 years for girls, and a Tanner pubertal stage of 4 or 5 (according to genitalia in boys and breasts in girls) at the time of their last height measurement. At these bone ages, more than 98 percent of adult height has been reached.¹⁵ Projected bone age was calculated by using the last measured bone age and assuming one year of advancement of bone age per calendar year.

The difference between the adult height and the predicted adult height before treatment in the children who received growth hormone was compared with the corresponding difference in two groups of normal children who were followed in the Fels Longitudinal Study with serial measurements of height and bone age until they reached adult height. These groups included 291 children with initial standard-deviation scores for height that were greater than -1 and bone ages of 10 years or less and 37 children with initial standard-deviation scores of less than -1 . In addition, we compared the difference between predicted and achieved adult height in the treated children with that in a group of children seen at the participating centers who had idiopathic short stature with initial standard-deviation scores of less than -2 and who were not treated with growth hormone. These children had achieved adult height, as judged by either bone age or lack of growth during more than one year of observation. Adult height in the three control groups was defined as either the last measured height or the last predicted adult height, whichever was greater. To be conservative, adult height in the children given growth hormone was defined as the last measured height.

Heights were standardized for age and sex with use of normal height curves for children in the United States.¹⁶ Predicted adult heights were calculated with the Bayley-Pinneau tables¹⁵ and a revised Bayley-Pinneau method of predicting adult height (unpublished data) for children with bone ages of three to six years. The midparental target height adjusted for regression to the mean was calculated from the average of the parents' heights, plus 6.55 cm for boys and minus 6.55 cm for girls.

Statistical Analysis

Ninety-five percent confidence limits were calculated for differences in means. Multiple linear regression analysis was used to determine which explanatory variables were linearly related to the difference between predicted adult height and actual adult height. The variables considered were base-line chronologic age, bone age, chronologic age minus bone age, standard-deviation score for bone age, height, standard-deviation score for height, predicted adult height, standard-deviation score for predicted adult height, peak stimulated serum growth hormone concentration, mean 12-hour nocturnal serum growth hormone concentration, serum growth hormone-binding protein, insulin-like growth factor I, and serum insulin-like growth factor-binding protein 3 concentration. In addition, sex, midparental target height, standard-deviation score for midparental target height, frequency of growth hormone treatment, duration of growth hormone treatment, and percentage of growth hormone doses reported to have been missed were also considered. There were no significant differences in adult height between children treated daily and those treated three times a week, or between the children who were given growth hormone in the first year and those who were not. Therefore, these groups were merged for the purposes of analysis.

RESULTS

Of the 121 children who entered the study, 80 have reached adult height, and all but 11 have now completed growth hormone therapy after up to 10 years. Fourteen children left the study because of noncompliance, 13 left the study for other reasons, and 11 were lost to follow-up. There were no side effects that required a change in the growth hormone dosage. The age, bone age, and standard-deviation score for height at base line and the duration of growth hormone therapy for the 80 children who reached adult height are shown in Table 1. Treatment with growth hormone resulted in a significant increase in the mean growth rate over the base-line growth rate, which was maintained for at least seven years (Fig. 1A). There was no significant change in the growth rate among the children who were not treated during the first year of the study,

TABLE 1. MEAN (\pm SD) BASE-LINE AND FINAL CHARACTERISTICS IN 80 CHILDREN WITH IDIOPATHIC SHORT STATURE TREATED WITH GROWTH HORMONE.

CHARACTERISTIC	BOYS (N=57)	GIRLS (N=23)
Base-line chronologic age (yr)	10.4 \pm 1.8	9.7 \pm 2.1
Base-line bone age (yr)	8.7 \pm 1.6	8.2 \pm 1.9
Base-line standard-deviation score for height	-2.8 \pm 0.5	2.7 \pm 0.4
Duration of therapy (yr)	6.0 \pm 1.7	5.5 \pm 1.7
Final height (cm)	165.5 \pm 7.2	153.1 \pm 4.8
Pretreatment predicted adult height (cm)	160.6 \pm 6.4	147.2 \pm 5.1
Final height minus pretreatment predicted adult height (cm)	5.0 \pm 5.1	5.9 \pm 5.2
Midparental target height (cm)*	170.7 \pm 4.5	159.0 \pm 3.4
Chronologic age at final height (yr)	18.1 \pm 1.6	17.2 \pm 2.0

*Data were missing for three boys.

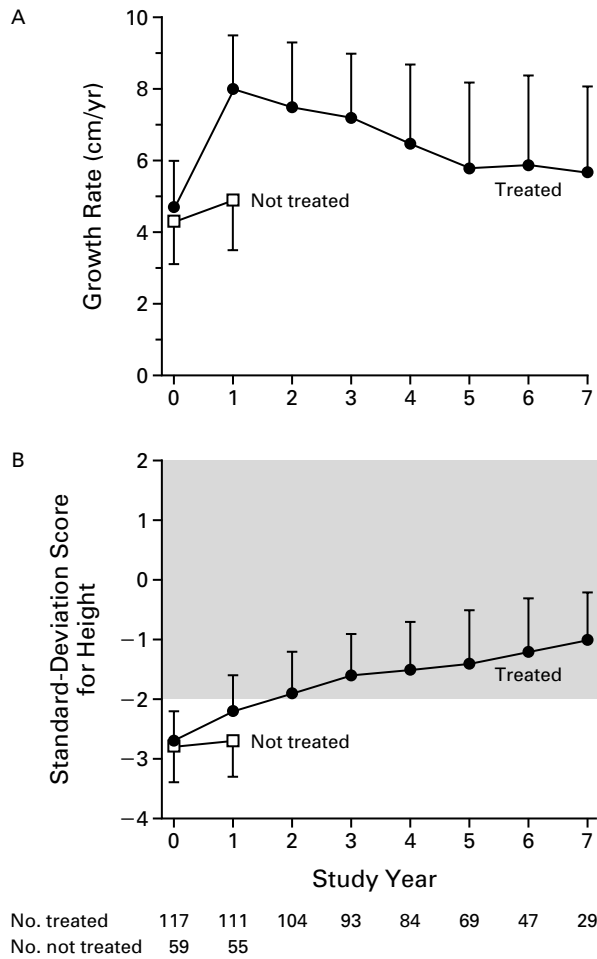


Figure 1. Effects of Growth Hormone Treatment in Children with Idiopathic Short Stature.

Panel A shows the mean (\pm SD) growth rate, and Panel B shows the mean (\pm SD) standard-deviation score for height. The value at time 0 is the growth rate for the preceding year or longer. The numbers below the graphs are the total numbers of children completing each year. Complete data for the pretreatment year were missing for 4 of the 121 children. Fifty-nine of the children were not treated in the first year, and their data are included both with the data for the untreated group and as part of the total data for the treated group. The shading in Panel B represents the normal range for height.

indicating that there was no effect of simply being enrolled in the study.

The mean base-line standard-deviation score for height for the 121 children with idiopathic short stature was -2.7 (Fig. 1B). The score in the 69 children treated for five years increased to -1.4 . The 29 children treated for seven years had a mean score of -1.0 .

The mean adult height of the 80 treated children was greater than the adult height predicted before treatment. In Figure 2, any point above the line of identity indicates an adult height greater than predicted. Although individual responses varied, 63 of

the 80 children (79 percent) had an adult height that was greater than predicted.

The mean (\pm SD) difference between the achieved and predicted adult height of the growth hormone-treated children was 5.0 ± 5.1 cm for boys and 5.9 ± 5.2 cm for girls (Table 1). Although the adult height of both boys and girls was greater than predicted, it was still less than the mean midparental target height. Both the pretreatment height and the predicted adult height were an average of 2.6 SD below the mean. After growth hormone treatment, the mean final height and final predicted adult height were both 1.6 SD below the mean. The mean target height for this group was 0.9 SD below the mean.

We compared the results in three historical control groups with those in the growth hormone-treated children. The normal boys in the Fels Longitudinal Study who had a base-line standard-deviation score for height that was greater than -1 achieved a mean adult height slightly (1.6 ± 5.4 cm) above their mean pretreatment predicted adult height (Fig. 3). The other group of boys in the Fels Study, with a base-line standard-deviation score of less than -1 , did not reach their mean pretreatment predicted adult height, being 1.7 ± 4.2 cm shorter. The trend toward overprediction of mean adult height in the boys was even more pronounced in the control group of untreated children with idiopathic short stature, who had base-line standard-deviation scores for height of less than -2 ; in this group, the mean difference between achieved and predicted adult height was 4.2 ± 7.7 cm. Of the 57 boys with idiopathic short stature who were treated with growth hormone, 45 (79 percent) exceeded their pretreatment predicted adult height, as compared with only 2 of 11 (18 percent) of the boys with idiopathic short stature who were not treated. In addition, 29 of the 57 boys (51 percent) with idiopathic short stature who were treated with growth hormone and only 1 of 11 untreated boys (9 percent) with idiopathic short stature had a clinically important (more than 5 cm) difference between actual adult height and adult height predicted before treatment.

The results among the girls were considerably different (Fig. 3). In the 147 normal girls in the Fels Study who had a base-line standard-deviation score for height that was greater than -1 , the pretreatment predicted adult height was less than the actual adult height, with a difference between actual and predicted adult height of 3.3 ± 5.4 cm; this was also the case in the 23 normal girls with a base-line standard-deviation score of less than -1 , in whom the difference was 3.6 ± 4.4 cm. In the 10 girls with idiopathic short stature who were not treated with growth hormone, the difference was 0.1 ± 2.9 cm. In the 23 girls with idiopathic short stature treated with growth hormone, 18 (78 percent) exceeded the adult height predicted before treatment. Only 1 of the 21 girls (5 percent) with idiopathic short stature

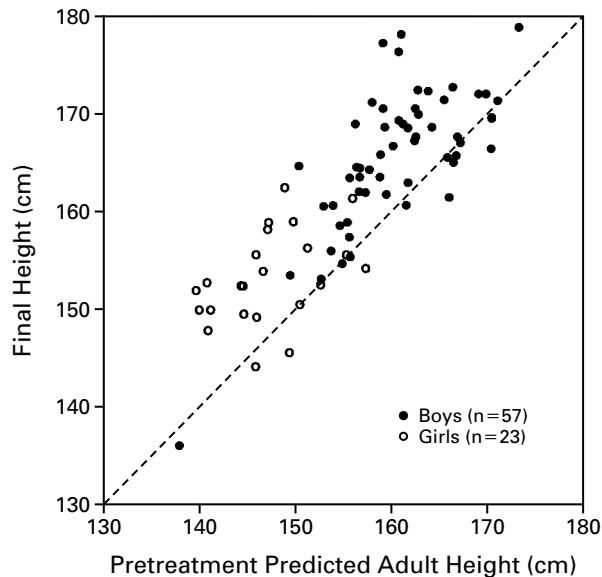


Figure 2. Final Height as Compared with Predicted Adult Height before Treatment with Growth Hormone in 80 Children with Idiopathic Short Stature Who Reached Adult Height.

who were not treated with growth hormone exceeded her initial predicted adult height by more than 5 cm, as compared with 14 of the 23 girls (61 percent) with idiopathic short stature who were treated with growth hormone. The overall mean changes seen with growth hormone treatment are summarized in Table 2. As compared with the results in the children with idiopathic short stature who were not treated with growth hormone, the mean increase in adult height was 9.2 cm for boys and 5.7 cm for girls with idiopathic short stature who were treated with growth hormone.

Since approximately half the children with idiopathic short stature who were treated with growth hormone had an adult height at least 5 cm greater than the height predicted before treatment, an important issue is whether a clinician can predict who is going to obtain substantial benefit from growth hormone therapy. We found no relation between the difference in the predicted and achieved adult height in the children treated with growth hormone and their pretreatment age, bone age, height, predicted adult height, peak serum growth hormone responses, 12- or 24-hour serum growth hormone concentrations, insulin-like growth factor I concentrations, serum growth hormone-binding protein concentrations, growth in response to the first 12 or 24 months of growth hormone treatment, or duration of treatment.

DISCUSSION

The majority of the children with idiopathic short stature enrolled in this study of growth hormone therapy had a significant increase in their growth

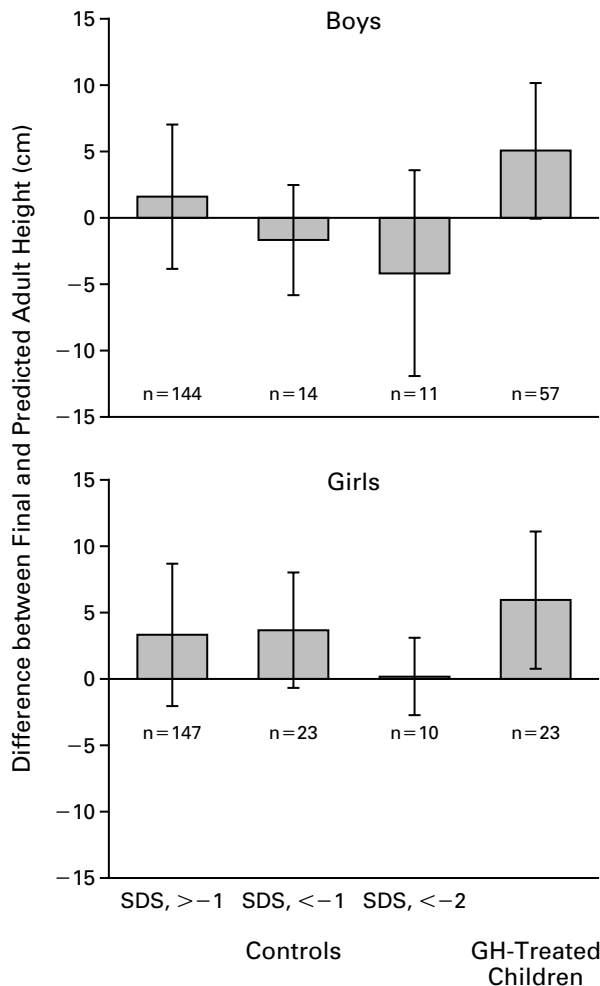


Figure 3. Mean (\pm SD) Final Height minus Predicted Adult Height before Treatment for the Three Control Groups and for Children with Idiopathic Short Stature Treated with Growth Hormone.

SDS denotes standard-deviation score for height, and GH growth hormone.

rate,¹¹ which was previously reported to persist for three years and was associated with an increase in the standard-deviation score for height and predicted adult height.¹² In this study, we found that the effect of growth hormone therapy on the growth rate was sustained and that it led to an increase in adult height. Of the 80 children in this study who have reached adult height after having received growth hormone for 2 to 10 years, 50 percent have reached a height more than 5 cm above the adult height predicted before treatment, but few have achieved their mean midparental target height.

These changes in adult height are consistent with the findings of some¹⁷⁻¹⁹ but not other²⁰⁻²³ studies of the effects of growth hormone treatment in children with idiopathic short stature. The differences in the

TABLE 2. DIFFERENCE BETWEEN ACHIEVED AND PREDICTED ADULT HEIGHT IN CHILDREN WITH IDIOPATHIC SHORT STATURE TREATED WITH GROWTH HORMONE AS COMPARED WITH TWO UNTREATED CONTROL GROUPS OF CHILDREN.*

VARIABLE	MEAN DIFFERENCE (95% CI)†	
	BOYS	GIRLS
	centimeters	
Value in children with idiopathic short stature treated with growth hormone‡	5.0 (3.6 to 6.3)	5.9 (3.7 to 8.1)
Value in children with idiopathic short stature treated with growth hormone minus value in control children (SDS less than -1)	6.7 (3.7 to 9.6)	2.3 (-0.6 to 5.1)
Value in children with idiopathic short stature treated with growth hormone minus value in control children (SDS less than -2)	9.2 (5.5 to 12.8)	5.7 (2.1 to 9.4)

*CI denotes confidence interval, and SDS the standard-deviation score for height.

†The mean difference was calculated as the final height minus the predicted adult height.

‡The group included 57 boys and 23 girls.

outcomes of these studies may be related to differences in the children studied. On average, the children in our study were younger at the beginning of growth hormone treatment and were treated longer than the children in many of the studies in which growth hormone treatment was not beneficial.

The calculated improvement in adult height in our study is dependent on both the reliability of the determinations of bone age and the validity of the predictions of adult height. The bone ages in this study were read in a masked fashion at the Fels Institute according to the Fels bone-age method.¹⁴ This method was validated in children of normal height and weight, but its applicability to children who are substantially shorter than normal is uncertain. The same is true of the Bayley–Pinneau height-prediction tables used in this study. Thus, we considered it important for the interpretation of our data to validate the use of the Fels method for bone age with the Bayley–Pinneau height-prediction method in children with varying degrees of short stature. The data from the Fels Longitudinal Study indicated that these methods are valid for boys of normal stature but overpredict adult height for short boys. This finding suggests that the net increase in adult height in the growth hormone–treated boys is a conservative estimate. The overprediction of adult height in boys with short stature has also been noted in several other studies,^{24–26} emphasizing the importance of comparisons with appropriate control data.

Unlike the findings in boys, the initial predicted adult height among normal girls in the Fels Study

significantly underestimated adult height, whereas the height prediction for girls with idiopathic short stature who were not treated was accurate.

The children with idiopathic short stature in this study had mean pretreatment heights and predicted adult heights that were more than 2 SD below the mean for chronologic age. The gains resulting from growth hormone therapy represent an average increase of approximately 1 SD in adult height. However, the mean adult height still remained substantially below the mean midparental target height. Furthermore, the responses to treatment in individual children were highly variable, and some had no apparent benefit.

The gains in adult height with growth hormone treatment in these children with idiopathic short stature are similar to those reported in another group of children with severe short stature, but without classic growth hormone deficiency — namely, girls with Turner’s syndrome.^{27–29} The similarity of the long-term growth response in these two groups suggests that other children with severe short stature who do not have growth hormone deficiency may have a similar response to growth hormone treatment.

Whether the increase in adult height in these children with idiopathic short stature treated with growth hormone is due to treatment of an abnormality of growth hormone secretion or action or to the pharmacologic effects of growth hormone is not known. The difficult questions of the ethical and financial justification of growth hormone treatment for these children with severe short stature must be faced squarely.³⁰ If there were no long-term benefit of treatment with growth hormone in children with idiopathic short stature, there would be no reason to treat and therefore no ethical problem. However, our study demonstrates that treatment may be effective. Thus, the decision to treat must involve a difficult judgment of the relative benefits, risks, and costs of the treatment.

Supported by Genentech and by grants (RR-06020 to Cornell Medical Center and RR-0865-24 to the University of California, Los Angeles) from the Public Health Service.

Presented in part at the annual meeting of the American Pediatric Society and the Society for Pediatric Research, San Diego, Calif., May 9, 1995. Dr. Hintz has served as a paid consultant to Genentech.

We are indebted to Mrs. Lily Brelsford, clinical research associate, Genentech, and the study coordinators at each center for their contributions to this study.

APPENDIX

Other members of the Genentech Collaborative Group were as follows: R. Blizzard (University of Virginia), J. Cara (University of Chicago), S. Chernausek (University of Cincinnati), M. Geffner (University of California, Los Angeles), J. Gertner (Cornell Medical Center), N. Hopwood (University of Michigan), S. Kaplan (University of California, San Francisco), B. Lippe (University of California, Los Angeles), L. Plotnick (Johns Hopkins University), A. Rogol (University of Virginia), P. Saenger (Montefiore Medical Center), G. Leboeuf (Hôpital Ste.-Justine), A.J. Johanson (Genentech), and J. Kuntze (Genentech).

Several members of the collaborative group are now or have been consultants to Genentech (Drs. Blizzard, Cara, Chernausek, Gertner, Hopwood, Kaplan, and Rogol), Eli Lilly (Drs. Gertner and Hopwood), Pharmacia-Upjohn (Dr. Geffner), and Serono (Drs. Cara and Rogol), makers of growth hormone, or to Biotechnology General (Dr. Rogol), maker of an anabolic steroid.

REFERENCES

1. Stanhope R, Hindmarsh PC. Hazards of tests of growth hormone secretion. *BMJ* 1992;304:777-8.
2. Marin G, Domene HM, Barnes KM, Blackwell BJ, Cassorla FG, Cutler GB Jr. The effects of estrogen priming and puberty on the growth hormone response to standardized treadmill exercise and arginine-insulin in normal girls and boys. *J Clin Endocrinol Metab* 1994;79:537-41.
3. Rose SR, Ross JL, Uriarte M, Barnes KM, Cassorla FG, Cutler GB Jr. The advantage of measuring stimulated as compared with spontaneous growth hormone levels in the diagnosis of growth hormone deficiency. *N Engl J Med* 1988;319:201-7.
4. Celniker AC, Chen AB, Wert RM Jr, Sherman BM. Variability in the quantitation of circulating growth hormone using commercial immunoassays. *J Clin Endocrinol Metab* 1989;68:469-76.
5. Rosenfeld RG, Albertsson-Wikland K, Cassorla F, et al. Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. *J Clin Endocrinol Metab* 1995;80:1532-40.
6. Van Vliet G, Styne DM, Kaplan SL, Grumbach MM. Growth hormone treatment for short stature. *N Engl J Med* 1983;309:1016-22.
7. Plotnick LP, Van Meter QL, Kowarski AA. Human growth hormone treatment of children with growth failure and normal growth hormone levels by immunoassay: lack of correlation with somatomedin generation. *Pediatrics* 1983;71:324-7.
8. Gertner JM, Genel M, Gianfredi SP, et al. Prospective clinical trial of human growth hormone in short children without growth hormone deficiency. *J Pediatr* 1984;104:172-6.
9. Hindmarsh PC, Pringle PJ, Di Silvio L, Brook CGD. Effects of 3 years of growth hormone therapy in short normal children. *Acta Paediatr Scand Suppl* 1990;366:6-12.
10. Takano K, Hizuka N, Asakawa K, Sukegawa I, Horikawa R, Shizume K. Effects of short-term growth hormone therapy in short children without growth hormone deficiency. *Acta Paediatr Scand Suppl* 1990;366:14-22.
11. The Genentech Collaborative Study Group. Idiopathic short stature: results of a one-year controlled study of human growth hormone treatment. *J Pediatr* 1989;115:713-9.
12. Hopwood NJ, Hintz RL, Gertner JM, et al. Growth response of children with non-growth-hormone deficiency and marked short stature during three years of growth hormone therapy. *J Pediatr* 1993;123:215-22.
13. Roche AF. Growth, maturation and body composition: the Fels Longitudinal Study 1929-1991. Cambridge, England: Cambridge University Press, 1992.
14. Roche AF, Chumlea WC, Thissen D. Assessing the skeletal maturity of the hand-wrist: Fels method. Springfield, Ill.: Charles C Thomas, 1988.
15. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. *J Pediatr* 1952;40:423-41. [Erratum, *J Pediatr* 1952;41:371.]
16. Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr* 1979;32:607-29.
17. Albertsson-Wikland K. Characteristics of children with idiopathic short stature in the Kabi Pharmacia International Growth Study, and their response to growth hormone treatment. *Acta Paediatr Suppl* 1993;391:75-8.
18. Zadik Z, Chalew S, Zung A, et al. Effect of long-term growth hormone therapy on bone age and pubertal maturation in boys with and without classic growth hormone deficiency. *J Pediatr* 1994;125:189-95.
19. McCaughey ES, Mulligan J, Voss LD, Betts PR. Randomised trial of growth hormone in short normal girls. *Lancet* 1998;351:940-4.
20. Bierich JR, Nolte K, Drews K, Brüggemann G. Constitutional delay of growth and adolescence: results of short-term and long-term treatment with GH. *Acta Endocrinol (Copenh)* 1992;127:392-6.
21. Loche 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.
22. Wit JM, Boersma B, de Muinck Keizer-Schrama SM, et al. Long-term results of growth hormone therapy in children with short stature, subnormal growth rate and normal growth hormone response to secretagogues: Dutch Growth Hormone Working Group. *Clin Endocrinol (Oxf)* 1995;42:365-72.
23. Hindmarsh PC, Brook CG. Final height of short normal children treated with growth hormone. *Lancet* 1996;348:13-6.
24. Ranke MB, Grauer ML, Kistner K, Blum WF, Wollmann HA. Spontaneous adult height in idiopathic short stature. *Horm Res* 1995;44:152-7.
25. Voss LD, Wilkin TJ, Bailey BJ, Betts PR. The reliability of height and height velocity in assessment of growth. *Arch Dis Child* 1991;66:833-7.
26. La Franchi S, Hanna CE, Mandel SH. Constitutional delay of growth: expected versus final adult height. *Pediatrics* 1991;87:82-7.
27. Rosenfeld RG, Frane J, Attie KM, et al. Six-year results of a randomized, prospective trial of human growth hormone and oxandrolone in Turner syndrome. *J Pediatr* 1992;121:49-55.
28. Nienhuis HE, Rongen-Westerlaken C, Wit JM, et al. Results of long-term treatment with growth hormone in two dose regimens in Turner syndrome. *Horm Res* 1993;39:Suppl 2:31-6.
29. Takano K, Shizume K, Hibi I, et al. Growth hormone treatment in Turner syndrome: results of a multicentre study in Japan. *Horm Res* 1993;39:Suppl 2:37-41.
30. Allen DB, Fost NC. Growth hormone therapy for short stature: panacea or Pandora's box? *J Pediatr* 1990;117:16-21.