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Growth Hormone Therapy in Childhood-Onset Growth Hormone Deficiency

Adult Anthropometric and Psychological Outcomes

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The current adult heights of hypopituitary children treated with recombinant human growth hormone (rGH) now range between –1.5 and –0.7 height standard deviations (Ht SDS) of control populations. These height outcomes are markedly better than the ones observed following treatment with pituitary-derived human growth hormone (pGH) (between –4.7 and –2.0 Ht SDS). Although treatment with rGH has not yielded adult heights that are equal to genetic target heights, the discrepancy is much less now than in previous decades. Higher rGH dose, longer duration of treatment, early age at diagnosis, correction of height deficit prior to onset of puberty, and daily rGH injections have had beneficial effects on final adult heights. The current dosing regimens (0.3–0.18 mg/kg/wk) have not had an adverse effect on bone maturation and have not stimulated an earlier onset of puberty. Although height gains in puberty are less than controls, a majority of treated subjects reach heights within the normal range for adults. Higher doses of rGH during puberty have been studied in limited numbers of adolescents with positive effects; however, standard dosing will likely continue to be used because of financial considerations and safety concerns. Further improvements in adult heights are likely to be reported when the youngest children who began rGH in 1985 complete their growth.

Several studies have investigated the quality of life (QOL) of GH-deficient (GHD) patients who, as children, had been treated with GH predominantly during the pGH era. Domains of functioning assessed include educational attainment, employment, and marital status. Although some studies have reported a generally positive adaptation, others have shown this group to exhibit marked deficits. Limited adult height outcomes in the pGH era of GH therapy has sometimes been used to account for poor outcomes. Variable behavioral findings are likely related to sample heterogeneity and disparate research methodologies and designs, most particularly the choice of control or comparison groups. In addition to summarizing this older literature, we report on a recently completed investigation in which the QOL adjustment of GHD patients is compared to that of same-sex siblings. Comparisons between GHD cases and norms for standardized questionnaires indicated both better and worse functioning in several domains. In contrast, very limited differences were detected between GHD cases and same-sex siblings. IGHD (isolated growth hormone deficiency) patients were functioning better than those with MPHD (multiple pituitary hormone deficiencies), but the effect sizes of these differences in most areas were relatively small. Adult height and degree of growth over the course of GH therapy were generally unrelated to QOL outcomes. Findings from the present study underscore the importance of selecting unbiased control/comparison groups in evaluating psychological outcomes among GHD adults.

Key Words: Growth hormone therapy; childhood-onset GH deficiency; height outcomes; adults; quality of life.

Introduction

Our knowledge about the effects of growth hormone (GH) treatment on adult heights of hypopituitary children is derived from approx 40 yr of clinical experience with both pituitary-derived (pGH) and recombinant human growth hormone (rGH) *(1–15)*. The pituitary GH era (1960–1985) was characterized by a nationally-funded program to collect human pituitary glands which were subjected to batch extraction until 1977. Thereafter, column purification was added to the production process. Throughout this 25 yr period, there were steady improvements in the quality of the GH, which resulted from using frozen human pituitaries rather than cadaver or acetone-preserved

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glands and better extraction techniques that provided less contamination and denaturation of the final product. However, the persistent problem was a constant shortage of pGH, which led to suboptimal dosing regimens, interrupted treatment periods, and strict criteria as to when GH treatment would be terminated. Initially treatment stopped when children reached a height of 5 ft, and later the cutoff height was extended to 66 in. It is not surprising, in retrospect, why many studies reported disappointing adult heights. These same studies also reported less than optimal psychosocial outcomes. Surprisingly, some investigators were inclined to question the overall efficacy of GH treatment, rather than the deficiencies of the treatment programs. This is understandable since there were no alternative GH treatment regimens that would provide comparative data. In early 1985, the deaths of three patients from Creutzfeldt–Jakob disease prompted the Food and Drug Administration to ban the use of pGH. In October of 1985, rGH was approved for distribution. The rGH era is relatively short but extremely informative in that we have begun to assess the true effects of GH on final height. The advantages of the rGH period include abundance of highly purified and precisely standardized product, freedom from interfering antibodies, and continuity of treatment without artificial cutoffs.

This article provides current information about the effects of rGH on adult heights, and to evaluate the quality of life outcomes of formerly-treated adults with childhood-onset GH deficiency (GHD).

Height Outcomes after GH Treatment

The variables that have been reported to impact on the efficacy of GH treatment include dose, age, and bone age at onset of treatment, treatment duration, pubertal status at onset of treatment, parental heights, frequency of GH injections, and compliance *(9–16)*.

During the pGH era, the range of mean adult heights of hypopituitary children who had completed GH treatment was between –4.7 and –2.0 standard deviation scores (Ht SDS) of adult controls *(1–5,12)*. In that period, the average dose of GH (0.1 mg/kg/wk or 0.3 IU/kg/wk) was approximately one-third of the dose being used currently. Also, the product used in that era was less well-standardized for biopotency, less pure, frequently not dosed on body weight, and given in a discontinuous manner depending on availability. Half of the treated population in one study never reached a normal adult height (> –2.0 SDS) and most of the remainder who attained normal height had failed to do so throughout their childhood years *(12)*. Despite these suboptimal growth responses, there were indications that treatment regimens could be improved upon if more attention was paid to standardizing the dose of GH according to body weight. Frasier and associates were the first to report on the advantages of using standardized doses of pGH; they observed a positive correlation between growth rate and the logarithm of the pGH dose over a dose range of 0.09–0.3 IU/kg/wk, which approximates 0.03–0.1 mg/kg/wk of rGH. The highest dose in their study was one-third of the dose of rGH being used currently *(17)*. A more recent dose-response study was done by the American Norditropin Trial Group using 0.025, 0.05, and 0.1 mg/kg/d of rGH in prepubertal, severely GHD children *(18)*. Significantly greater growth velocities and greater gains in cumulative Ht SDS resulted from 0.05 mg/kg/d compared to 0.025 mg/kg/d during 2 yr of observation. The highest dose of GH (0.1 mg/kg/d) yielded growth responses that were comparable to those observed in the group receiving 0.05 mg/kg/d. The mean Ht SDS after two treatment years were not significantly different in the 0.05 and 0.1 mg/kg/d treatment groups (–0.9 and –0.7, respectively) ; both groups attained a significantly better mean Ht SDS compared to the group given 0.025 mg/kg/d (–2.0 Ht SDS).

There is unanimous agreement about the optimal treatment goals for hypopituitary children receiving rGH therapy *(13,19)*. These include correcting the height deficit in early childhood, avoidance of over- or undertreatment, insuring that age at onset and height gains of puberty are normal, attainment of normal adult height at an appropriate age, attainment of final height compatible with midparental target height, and avoidance of adverse effects due to GH therapy.

Adult heights of hypopituitary children who were treated almost exclusively with rGH since 1985 are shown in **Table 1**. The rGH dose was either 0.3 or 0.18 mg/kg/wk given subcutaneously; for many years, three injections were given each week. The data provide information about two important variables: dose and duration of rGH treatment. The mean adult heights in the four studies ranged from –1.5 to –0.7 Ht SDS; they are significantly greater than those observed after pGH treatment. The greatest gains in Ht SDS and the tallest adult heights were seen in Group 1, which was comprised of hypopituitary children treated with 0.3 mg/kg/wk of rGH for a total of 6–8 yr (5.7 and 6.4 yr of only rGH for girls and boys, respectively) *(9)*. The mean adult heights in Group 2, who received 0.19 mg/kg/wk of rGH, were less than Group 1 even though the duration of treatment in this group (6.8 yr and 6.4 yr for boys and girls, respectively) was similar to Group 1 *(10)*. At the start of rGH treatment, the children in Group 2 were somewhat younger and less growth retarded than the subjects in Group 1, yet these advantages did not yield greater adult heights. Consequently, the improved adult height outcomes seen in Group 1 appear to have resulted from the positive effects of using a higher rGH dose. The other two groups, Groups 3 and 4, give information about the effect of duration on height outcomes; both of these groups were treated with 0.3 mg/kg/wk of rGH but mean age at onset of

Table 1
Effects of rGH Dose, Age at Onset, and Duration of Treatment on Adult Heights of Hypopituitary Children

	Group 1 (9) Mean		Group 2 (10) Median		Group 3 (11) Mean		Group 4 (12) Mean
	Male	Female	Male	Female	Male	Female	Both Sexes
n	72	49	66	64	480	194	95[a] (14[b])
Age at start of GH treatment, yr	11.3	10.6	10.5	9.9	12.7	11.2	13
Height SDS at start of GH treatment	–3.0	–3.4	–2.7	–2.9	–2.6	–3.0	–2.7
BA SDS at start of GH treatment	–3.0	–3.1	—	—	–2.6	–3.0	–2.3
GH (mg/kg/wk)	0.3	0.3	0.19	0.19	0.3 (approximate, for boys and girls)		0.3
Final height SDS	–0.7	–0.7	–1.3	–1.2	–1.3	–1.6	–1.5
Total years of GH treatment	6.4	5.7	6.8	6.4	4.6	4.3	3.8
Final height (cm)	171.6	158.5	166.0	154.9	168.3	154.0	166.9[a] (153.4[b])
Total increase in height SDS	2.3	2.7	1.4	1.7	1.3	1.4	1.3[a] (1.3[b])

BA indicates bone age. In group 4, [a] = males, [b] = females.

GH therapy was older *(11,12)*. Consequently, the mean duration of rGH treatment was shorter; i.e., 4.6 yr and 3.8 yr for Groups 3 and 4, respectively. The height outcomes in Groups 3 and 4 were comparable (168.3 cm. vs 166.9 cm. for males in Groups 3 and 4, respectively; 154 and 153.4 cm. for girls in Groups 3 and 4, respectively). These data illustrate the impact of duration of treatment on adult heights when dose is kept constant *(11,12)*.

The current dosing regimens of rGH do not appear to accelerate the pace of bone maturation in childhood, nor to trigger early onset of puberty *(11,12,14,15)*. While this generalization is considered true for rGH doses in the approved range (0.18–0.3 mg/kg/wk), it may not be valid for higher doses. Also, individual children with unusual sensitivity to standard rGH dosing regimens may exhibit excessively rapid growth and above normal serum IGF-I levels. More conservative rGH dosing is required for these subjects in order to avoid iatrogenic acromegaloid features *(20)*.

The effects of rGH dose on the mean age at onset of puberty are shown in **Table 2** for the same four study groups *(9–12)*. At onset of puberty, mean age was within the normal range and was similar in the four groups; it did not appear to be influenced by prior rGH dose. Also, the mean bone ages at onset of puberty were similar among the groups except for slightly older bone ages in the girls in Group 2. Mean Ht SDS at onset of puberty was highest in Group 2 and lowest in Group 4. The former was due to the young age at onset of rGH treatment, while the latter resulted from the late age at diagnosis. The pubertal height gains (cm) ranged between 22 and 24.9 for males and 15 and 19.4 for females, which is less than the reported pubertal height gains seen in control children *(21)*. The increase in Ht SDS during puberty was greatest in Group 1 (1.4), least in Group 2 (0.3), and intermediate in Groups 3 and 4 (0.8 and 1.1, respectively). These differences in delta Ht SDS may be more apparent than real since the actual height in centimeters were more comparable among the groups. Surprisingly, the height gains with rGH treatment are similar to that reported in one study from the pGH period, which used one-third of the rGH dose. Taken together, these observations suggest that it is primarily sex steroids and, to a lesser extent, GH dose that determine the pubertal gain in height *(22)*. If additional evidence supports our findings on the equivocal effects of rGH on growth during puberty, we assume that doses of rGH in excess of 0.3 mg/kg/wk may not be indicated during adolescence. Nevertheless, we need to be cautious about this conclusion since the height gains of puberty were uniformly less than normal in all groups of hypopituitary children regardless of GH dose. Other investigators have recommended that hypopituitary adolescents receive higher doses of rGH (in excess of 0.3 mg/kg/wk) since normal puberty is characterized by markedly augmented GH production due to higher amplitude of GH pulses. In one study, pubertal GH-deficient subjects given a dose of 0.7 mg/kg/wk gained an additional 4 cm of height and had greater Ht SDS after 30 mo of rGH treatment compared to the group receiving 0.3 mg/kg/wk. Bone matura-

Table 2
Effect of rGH Dose on Age at Onset of Puberty and on Pubertal Height Gains

All Patients	Group 1 (9)	Group 2 (10)	Group 3 (11)	Group 4 (12)
n = All subjects (females)	84 (38)	130 (64)	674 (194)	82 (11)
Age at start of GH therapy, yr (females)	11.3 (10.6)	10.5 (9.9)	12.7 (11.2)	13.1
Height SDS at start of GH therapy (females)	–3.0 (–3.4)	–2.7 (–2.9)	–2.6 (–3.0)	–2.8
Dose of GH (mg/kg/wk)	0.3	0.19	0.3	0.3
Males, onset of puberty				
Age (mean, yr)	14.0	13.8	14.1	14.1
Height SDS	–2.1	–1.6	–2.1	–2.6
BA (mean, yr)	11.8	12.0	11.9	11.6
Pubertal height gain (mean, cm)	24.9	22.0	22.4	23.5
Females, onset of puberty				
Age (mean, yr)	12.6	12.9	12.6	12.4
Height SDS	–2.0	–1.4	–2.4	–2.9
BA (mean, yr)	10.3	11.4	10.6	9.8
Pubertal height gain (mean, cm)	19.4	15.0	17.4	19.1
Delta Ht SDS during puberty	1.4 (1.3)	0.3 (0.2)	0.8 (0.8)	1.1 (1.1)
Final height outcome, SDS	–0.7 (–0.7)	1.3 (–1.2)	–1.3 (–1.6)	–1.5 (–1.8)
Duration of GH therapy, yr (females)	6.4 (5.7)	6.8 (6.4)	4.6 (4.3)	3.8

BA indicates bone age. Male and female data combined in Group 4. All numbers in parentheses refer to females.

tion was similar in the two groups and both doses were well-tolerated *(23)*.

During the past 14 yr, the frequency of rGH administration has increased significantly. Most investigators now recommend rGH injections be given daily (or at least five times weekly) rather than three times weekly. The much improved growth that resulted from a daily rGH treatment regimen was observed in a study of exclusively prepubertal hypopituitary children; the effects of the daily dosing schedule in that study was not followed throughout puberty to adult heights *(24)*. It was assumed that the taller heights at onset of puberty in hypopituitary children given daily rGH would translate to greater adult heights. A recent presentation by Cutfield and colleagues confirm that frequency of rGH therapy has a positive effect on adult height outcomes *(14,15)*. In their study of 223 males and 146 females with idiopathic GH deficiency who had received approximately five injections of rGH weekly and who had a minimum of two years of rGH treatment prior to onset of puberty, the adult heights achieved for males and females were –0.85 and –1.2 Ht SDS, respectively. Duration of therapy was approx 8 yr. Using multiple regression analysis, the variables that had a positive effect on adult heights were taller parents, more frequent rGH injections, longer duration of rGH treatment, taller heights at start of rGH treatment and greater severity of GH deficiency.

Since our current assessments of adult heights are limited to approx 14 yr of experience with rGH treatment of hypopituitary children, we have had to rely on a database that is comprised entirely of older subjects who are now adults. During the next decade, we are likely to attain the goals of having rGH-treated hypopituitary children reach their midparental heights and have a normal distribution of adult Ht SDS; success will depend on early diagnosis of GH deficiency and normalization of height prior to onset of puberty. This optimistic prediction is based on the belief that better adult height outcomes will be seen in the youngest children who began rGH after 1985 and are yet to reach their adult heights.

Quality of Life (QOL) Among Formerly Treated Child-Onset Growth Hormone-Deficient (GHD) Adults

One important therapeutic goal of GH therapy in childhood-onset GHD has been the normalization of height during both childhood and adulthood in an effort to optimize the individual's QOL. In view of the improvements in adult height outcomes brought about by the introduction of rGH, it is easy to understand why clinicians might expect that the psychosocial adaptation of individuals treated entirely in this new era will be superior to that of patients who were treated when supplies of pGH were limited. Until there are a larger number of patients who have been treated from a young age exclusively in the rGH era of therapy, there remains much to be learned about the QOL outcomes of patients who have completed GH therapy, regardless of the era in which it was received.

Nine studies conducted since 1985 have focused on the psychosocial adaptation of formerly treated patients with childhood-onset GHD *(2,3,26–32)*. Studies of the benefits of continuing GH replacement in adulthood are not included. The nine studies vary markedly in terms of sample sizes, the final adult height achieved with treatment, and

the research design and statistical analyses used to assess QOL outcomes.

Educational Attainment and Intelligence

Educational attainment among formerly treated GHD patients has typically been shown (but not without exception, e.g., ref. *31*) to be comparable to unaffected siblings and general population norms. Although not consistently addressed in data analyses, most of these studies have also not detected differences in the level of attainment of individuals with isolated GHD (IGHD) compared to those with multiple pituitary hormone deficiencies (MPHD) *(3,26,32)*, despite the fact that the intellectual potential of MPHD patients appears to be lower than in IGHD cases *(28,33)*. In a different, but likely overlapping partitioning of GHD cases, Dean et al. *(2)* did not detect a difference in educational attainment between those with idiopathic vs organically based GHD. In an uncontrolled study, Frisch and colleagues *(30)* reported that 47% of their sample (n = 48; ages 16–26 yrs) had repeated a grade in school. The median IQ of the GHD sample was 105 (range = 75–122) if those cases (n = 8) with physical disabilities (related to brain tumor, visual deficits) were excluded from analyses. Correlations between IQ and duration of GH therapy or Ht SDS were not detected.

Employment

A review of employment patterns revealed a somewhat different and less optimistic picture. Several studies found higher rates of unemployment or underemployment among GHD patients compared to norms or comparison groups *(2,26,27)*, although there were exceptions *(3,31,32)*. Employment status *(2)* and income *(31)* were unrelated to final, adult height of former patients, but it was suggested that GHD patients may occupy lower status occupations *(26)*. This observation might be related to the experience among those GHD patients who had achieved a relatively poor adult height outcome and who reported that they experienced height-related discrimination when applying for jobs *(30,31)*. Finally, no consistent difference was found in employment status of IGHD vs MPHD patients: two studies *(2,32)* did not detect employment rate differences, whereas a third study *(28)* found that IGHD occupied higher status occupations than MPHD cases. Patients with idiopathic GHD were employed in the same proportion as those with organic GHD *(2)*.

Marital Status

The QOL outcome of marital status has been systematically assessed across several follow-up studies. For those studies in which comparison statistics were available, GHD patients were less frequently married *(2,28,31,32)*. This effect appeared to be more pronounced among MPHD than IGHD cases in some studies *(3,31)* but not in others *(26,32)*. After controlling for treatment, demographic variables, and other individual characteristics, hypogonadotropism was not found to be predictive of lower marital rates *(2)*. Examining a related aspect of QOL, several investigators have suggested that formerly treated GHD patients are more likely to be living with parents or relatives than living independently *(2,3,26,30,32)*. Pituitary status (i.e., IGHD vs MPHD) was not systematically related to this outcome across studies.

Beyond the QOL outcomes summarized above, individual studies have assessed additional domains of adaptation. Some of these studies have incorporated control/comparison groups into their designs whereas others have relied upon norms for the questionnaires selected. In general, GHD subjects score poorly relative to norms *(29–31)*, although exceptions have also been reported *(27,30)*. Interestingly, final height was not significantly correlated with any of the adult outcome variables *(2,26,31)*.

Research Design/Methodological Weaknesses

Several problems exist in this follow-up literature that make it difficult to interpret the findings. First, selection criteria for subject eligibility are not always explicitly stated and vary across studies. Several studies give only limited information concerning both inclusion and exclusion criteria (e.g., diagnostic criteria for GHD using GH provocative tests). Other studies do not permit the reader to know if individuals with medical problems in addition to the pituitary deficiency remain within the sample frame. Obviously, the inclusion of such cases (e.g., individuals with blindness) could potentially confound the interpretation of various behavioral outcomes.

Previous studies have also commonly relied upon a postal survey methodology that provides little control over the circumstances under which (and by whom) forms are completed. An alternative would be telephone interviews that are equivalent to in-person interviews in terms of reliability, validity, precision of estimates, and response rates *(34,35)*.

Given the amount of attention directed in the endocrine management of individuals with GHD toward improving growth velocity and optimizing adult height, it is surprising that only three of the nine cited QOL studies assessed the relationship between final height and psychosocial outcomes *(2,26,31)*, and then, for only selected dependent variables.

Finally, the aforementioned studies provide a broad mixture of control and comparison groups against which the psychosocial adaptation of the GHD samples are evaluated. In some studies, and for some measures, no comparisons to physically healthy control subjects are provided; thus the results are of a totally descriptive nature (e.g., ref. *27*). In other cases, "population" norms are invoked for an estimation of expected demographic parameters within the GHD sample without adjusting for differences in poten-

tially influential background differences, such as socioeconomic level, between the clinic-based sample and the general population (e.g., ref. *3*). Along the same lines, questionnaire norms are adopted for comparison purposes with little consideration given to the suitability of such norms (e.g., ref. *29*). Differences between the clinical and normative samples in terms of age, gender, socioeconomic status, or otherwise, could easily result in spurious differences. Although an attractive alternative to "norms," the potential methodological benefits of utilizing a healthy sibling control group has not been maximized in previous studies because same- and opposite-sex siblings of varying ages are apparently lumped together with data derived from proxy reporting by patients or parents rather than from the siblings themselves *(26,27,29)*.

In the case of statistical comparisons between subgroups of GHD patients (e.g., IGHD vs MPHD), analyses do not adjust for potential background differences (e.g., age, gender, socioeconomic status) between the groups that could influence the results.

We have recently reported findings of a study that revisits the question of the adult psychosocial adjustment of formerly treated child-onset GHD individuals, but does so in a relatively large and endocrinolgically well-defined GHD sample *(36)*. Telephone administration of well-standardized questionnaires was introduced as a methodological innovation in order to enhance both the reliability and validity of the data collected. In addition to comparisons with published norms for the selected questionnaires, this study was the first to directly contrast the adaptive functioning of GHD patients to unaffected, same-sex siblings. Additional questions addressed included the relationship between adult height, patient diagnosis, and QOL.

QOL in Formerly Treated Childhood-Onset GHD patients (the Buffalo, New York Experience)

All formerly treated GHD patients from one endocrinology program at a regional pediatric hospital in a moderately sized city in the northeastern U.S. who were at least 18 yr or older at the start of the follow-up study were eligible (n = 212). Prior to the initiation of treatment, all had exhibited a peak GH response to two standard provocative GH stimulation tests of <10ng/mL (polyclonal antibody) prior to initiating therapy*. Patients with mental retardation or a chronic physical disability/disease (e.g., blindness, insulin-dependent diabetes mellitus) (n = 17) were excluded from the sample frame. An additional 10 cases were deceased at the time of the follow-up. Of the remaining 185, there were 45 cases (24.3%) that were either lost to follow-up, did not respond to repeated requests by mail to participate, or refused. A total of 140 former patients (76%; 117 males, 23 females) participated. The mean age at follow-up was 26.1 (±6.5) years (range: 18.8–46.9 yrs). A total of 95 subjects had IGHD and 45 exhibited MPHD.

Of the 140 GHD patients eligible and agreeing to participate, a total of 63 subjects had an unaffected, same-sex sibling 18 yr or older; 53 siblings (84%) participated in the study. Their mean age at follow-up was 29.7 (±7.6) years (18.4–52.9 yrs). Forty-one (77%) of the GHD-sibling pairs were male. Because the same-sex siblings were significantly older than the GHD cases at the time of the study, data analyses statistically controlled for subject's age. Further details regarding data analyses are provided elsewhere *(36)*. Selected diagnostic and treatment-related anthropometric variables are summarized in **Table 3**.

The study was conducted as a telephone interview in which the majority of interviews with GHD cases (78%) and siblings (87%) were conducted blind to the subject's clinical status. Replicating earlier studies *(2,3,26–28,32)*, the educational attainment of GHD patients appears unaffected by clinical status (i.e., GHD vs healthy, same-sex sibling). This observation is particularly noteworthy in view of findings from other studies indicating that subgroups of GHD patients exhibit lower IQ scores *(28,33)* and/or cognitive deficits *(6,37)*. These latter effects might be related to the observation that GHD patients are at risk for experiencing academic underachievement and grade retention (for review, *see* ref. *38*). The apparent discrepancy between the different sets of findings might be understood as indicating that GHD is a better predictor of academic achievement during the early years of schooling than it is of the *ultimate* level of educational attainment. Early academic challenges may be successfully ameliorated through specialized remediation. Because data concerning early educational and remedial experiences were not collected, this hypothesis remains untested. Recent findings from a separate study, however, support this notion *(39)*.

A comparison between GHD cases and sibling controls also did not reveal differences in the proportions of each group who were gainfully employed at the time of the study, or who were living independently from parents or other relatives. Significantly fewer GHD cases than siblings were married, however. More will be said about this finding later.

When GHD cases were compared to general population norms for the SF-36 Health Survey *(40)*, a generic health-related QOL measure, an unexpected finding emerged: former patients scored higher (indicating *better* functioning) on two of eight scales, without any significant differences in the opposite direction. In contrast, a comparison of GHD cases with norms for the Brief Symptom Inventory (BSI) *(41)*, a measure of psychological distress, revealed much higher symptom rates within the patient group. A more consistent and interpretable picture devel-

*Data analyses did not reveal a statistically significant relationship between peak GH response to provocative stimulation tests and scores on the dependent variables.

Table 3
Selective Diagnostic and Anthropometric Variables for the Total GHD Sample and Subset of Patients with a Same-Sex Sibling Participating in the Study

Variable	Total GHD Sample (n = 140)	GHD Sample with Participating Sibling (n = 53)
Isolated GHD (vs MPHD) (%)[a]	67.9%	58.5%
Idiopathic GHD (vs Organic) (%)	87.1%	83.0%
Age at start of GH therapy (years)		
Mean	12.3 yr	12.2 yr
SD	3.4	3.5
Range	2.6 to 18.1	2.6 to 18.1
Height at start of GH therapy (SD)		
Mean	–3.1 SD	–3.2 SD
SD	1.2	1.3
Range	–7.2 to –0.5	–7.2 to –0.5
Duration of GH therapy (years)		
Mean	4.5 yr	4.5 yr
SD	3.1	3.3
Range	0.9 to 14.3	0.9 to 14.3
Final height (SD)		
Mean	–1.5 SD[b]	–1.5 SD[c]
SD	1.0	1.0
Range	–4.7 to 0.8	–4.7 to –0.1
Change in Height Over Rx (SD)		
Mean	1.6 SD[b]	1.7 SD[c]
SD	1.2	1.3
Range	–2.0 to 6.0	–2.0 to 5.1

[a]Abbreviations: IGHD = isolated growth hormone deficiency; MPHD = multiple pituitary hormone deficiency.
[b]n = 132.
[c]n = 51.

oped from comparisons between GHD cases and same-sex siblings. In the case of both the SF-36 and BSI, there were very limited differences between the groups. The one statistically significant difference that did emerge was predictable and relatively easy to understand: the GHD cases reported more problems than siblings on the General Health scale of the SF-36. *These findings suggest that the choice of control or comparison groups in studies of GHD patients can have profound effects on the results and thus the conclusions drawn from the study*.

The importance of selecting appropriate control/comparison groups for behavioral studies of GHD patients has been discussed elsewhere *(42)*. We favor those comparisons utilizing same-sex siblings because of the greater ability to control for genetic and social–environmental factors within individual families, which could influence the psychosocial adaptation as assessed by the questionnaires used in this study. An alternative interpretation of the relative equality of the GHD and sibling groups posits that the siblings were themselves experiencing problems of adjustment (e.g., on the BSI) that masked the difficulties experienced by the GHD group. Increased problems in the control group would be conceptualized as stress-related and stemming from the presence of a sibling with a chronic medical problem. Weakening this argument, the empirical literature on this subject has not consistently demonstrated an association between having a sibling with a chronic illness and psychological maladjustment *(43)*. Furthermore, speculation that the siblings in this study were maladjusted conflicts with their self-reports of *better* adjustment compared to norms on the SF-36, a measure of health-related QOL.

On measures of social support and adjustment *(44,45)*, there were no differences between GHD cases and sibling control subjects. How then is one to understand the significantly lower marital rates among GHD cases when compared to siblings, despite the overall equivalence in functioning across a wide range of psychosocial measures? Supplementary statistical analyses assessing the potential influence upon marital status of within-group (GHD) variables such as final height, gonadotropin deficiency, compliance with the sex hormone replacement regimen when applicable, and etiology of GHD (i.e., idiopathic vs organic), did not reveal an explanation. Increased change in relative height from the start of treatment until final height was significantly predictive of marriage for the subgroup of GHD patients with a same-sex sibling (i.e., those patients who had grown more were more likely to be married

at follow-up). This effect could not be replicated, however, in the remainder of the GHD sample without a same-sex sibling. Adult height was not correlated with marital status within the GHD sample. Further research is thus needed to explain why, in this and several other studies, marriage rates for adult GHD patients are lower than expected despite apparent similarities between GHD and non-GHD cases on several other indices of psychosocial adjustment. Complicating the picture further, a recently published study reported that patients with "idiopathic short stature" (i.e., GH-sufficient short stature) who were treated with GH were less likely to have a "partner" than patients with the same diagnosis who were not treated *(46)*, although no difference with the general population was detected. These authors speculate that "long-term rhGH treatment might delay the development of independence in adolescence."

IGHD and MPHD patients could not be differentiated based upon educational attainment, percentage employed, or marital or living status. Similar findings have been reported in some studies *(2,3,26,32)* but not in another *(31)*. In contrast, the IGHD patients described themselves as higher functioning than patients with MPHD. The effect sizes of the group differences on five of eight SF-36 QOL scales, although statistically significant, were relatively small (between 2.8% and 7.8% of the variance in scale scores). The IGHD group also reported more positive self-perceptions regarding their integration within a network of peers and involvement in spare-time activities. These findings contrast with those of Björk and colleagues *(29)* who did not detect differences between these subgroups on similar measures, although their sample size was substantially smaller ($n = 23$) than in the present study. In the area of emotional distress, as assessed by the BSI, the MPHD subgroup reported more distress on only one scale, *Somatization*. This difference should be interpreted cautiously. The *Somatization* scale is designed to assess distress arising from perceptions of bodily dysfunction in generally healthy individuals. The higher scores among the MPHD than IGHD patients may reflect true differences in somatic symptoms attributable to the patient's clinical status rather than a tendency to somatize psychological difficulties. One potential explanation for the differences in functioning between the IGHD and MPHD subgroups involves MPHD patients' compliance with recommended hormone replacement regimens. One of the items included in the telephone interview concerned self-ratings of compliance. Statistically significant correlations between these self-ratings of compliance and scores on the outcome variables were not detected. In view of the common observation that adherence to medical regimens is typically far from perfect, future studies ideally will include laboratory assessments to verify patients' self-reports.

One of the goals of GH therapy for GHD is to allow the child to achieve his/her full genetic growth potential. Furthermore, it is often assumed that increases in growth velocity and adult height will translate into enhanced QOL *(25)*. Findings from previous studies *(2,26,31)* do not support the presence of a statistically significant relationship between adult height and psychosocial adjustment. The present study generally confirms this in a relatively large and complete sample of GHD patients. Although final height (but not change in relative height over the course of therapy) was related to a limited set of variables, the effect sizes were rather small (between 2% and 3% of the variance in outcome scores). This was the case despite the very wide range in adult heights for the two eras combined (from –4.7SD to +0.8SD) and changes in delta Ht SDS with treatment (–2.0SD to +6.0SD). It would thus appear that maximizing adult height outcomes may not automatically translate into improved QOL outcomes. This statement should not be interpreted as suggesting that GH treatment was ineffective in enhancing patients' QOL as adults. In order to make such a statement, one would need to compare *treated* and *untreated* GHD patients after a similar follow-up, an option which is both unrealistic as well as unethical. On the other hand, the observation that GH-induced increases in relative height are not associated with improved psychosocial adjustment may be relevant to the ongoing debate regarding the benefits of providing GH to short-stature patient groups who do not exhibit clear evidence of a GHD state *(46,47)*. In such cases, the subjective value ascribed by the individual (and/or family) to taller adult height may influence the treatment decision. Another factor that should be considered in evaluating the psychological outcomes of our particular cohort of patients is that all had access to mental health services available through a psychoendocrine program that is fully integrated within the clinical service providing endocrine care *(38)*. This close collaboration among professionals representing medical, psychological, and educational/vocational disciplines perhaps has contributed to the generally positive outcomes of our patients, an effect that surmounts the possible influence of adult height.

What relevance, if any, do these findings hold for current discussions regarding the practice of continuing GH replacement therapy in adulthood? Insofar as our cohort of GHD patients were not retested for GHD in adulthood, it is unclear what proportion would be eligible for treatment employing the typically stringent criteria adopted in studies of GHD in adulthood *(48)*. In all likelihood, the majority of the MPHD patients in our study would retest GHD as adults and this subgroup did exhibit more problems of psychosocial adaptation than those with IGHD. Another distinction between our sample and those typically involved in clinical trials of GH replacement in adulthood is that our patients exhibited *childhood-onset* GHD. A recent report indicates that individuals with GHD of *adult onset* are more severely impacted, psychologically and metabolically, by

their clinical status. They, in turn, may benefit from replacement of GH in adulthood to a greater degree than individuals with childhood-onset GHD *(49)*. Insofar as that study combined patients with IGHD and MPHD of childhood onset, it could be the case that there is a subgroup of childhood-onset GHD patients who would benefit from the continuation of rGH therapy in adulthood as much as individuals with adult-onset GHD. These would most likely be the MPHD cases who, from our own and others' studies, appear to be most severely affected from a QOL standpoint.

Research on the topic of QOL among children or adults with GHD is necessarily interdisciplinary and thus requires the expertise of individuals from multiple specialities. The challenge for clinical researchers in this area is to ensure that the endocrine and psychoendocrine components of such interdisciplinary research meet comparably high standards.

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