Adult Height in Growth Hormone Deficiency: Historical Perspective and Examples From the National Cooperative Growth Study

J. Paul Frindik, MD*, and Joyce Baptista, MA‡

ABSTRACT. There are few historical data on final or adult heights after the completion of long-term growth hormone (GH) therapy in children with GH deficiency (GHD). Adult height has been defined as that achieved at chronologic ages ranging from 18 to 30 years, at bone ages ≥13 years (girls) and ≥15 years (boys), at growth velocities ≤1 to 2 cm per 6 to 12 months, at the “cessation of growth,” at “1 year after the completion of pubertal development,” and that at which patients are either “satisfied with their height” or have attained an “accept adult stature.”

Without GH treatment, children with GHD have a mean adult height standard deviation score of −4.7 (range, −6.1 to −3.9). After treatment, the standard deviation score range from −4.7 to −1.2 (pituitary GH [pitGH] 2–4 times a week) and from −1.4 to −0.5 (recombinant human [rhGH] GH 3 times a week to daily) in women and from −3.6 to −1.1 (pitGH) and from −1.3 to −0.7 (rhGH) in men. Because there is no uniformly applied definition of adult height, comparisons are difficult, but historical data suggest that posttreatment heights are greater with rhGH than with pitGH.

Using the National Cooperative Growth Study database, we found that the criteria used to define adult height affected the apparent outcome. When chronologic age ≥20 years for men and ≥18 years for women was the only criterion, 27% of patients grew ≥5 cm after having reached this age. Adding the requirement of advanced puberty before adult height could be considered to have been attained reduced the proportion of those who later grew ≥5 cm to <10%, but also decreased the number of patients available for analysis. A combination of criteria for adult height (chronologic and bone age ≥16 years for boys and ≥14 years for girls plus advanced puberty plus growth rate of <2 cm per year) left only 1% of patients with later growth of ≥5 cm. Pediatrics 1999;104:1000–1004; adult height, growth hormone, growth hormone deficiency.

Abbreviations. GH, growth hormone; GHD, GH deficiency; SDS standard deviation score(s); NCGS, National Cooperative Growth Study; rhGH, recombinant human GH; CA, chronologic age; BA, bone age; pitGH, pituitary GH; NAH, near adult height.

From the *Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas; and ‡Medical Affairs, Genentech, Inc, South San Francisco, California.

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METHODS

In this report we review published data on the heights of patients with GHD and emphasize the difficulties in defining adult height. Historical height data are presented as standard deviation score(s) (SDS). If the original publication did not give the height measurements as SDS, they were converted to SDS by using National Center for Health Statistics data.

We then apply various historical definitions of adult height to assess the growth in patients with GHD who are treated with GH in the National Cooperative Growth Study (NCGS), a postmarketing surveillance program established in 1985 to monitor the use, safety, and effectiveness of recombinant human GH (rhGH) made by Genentech, Inc (South San Francisco, CA). Methods of subject enrollment and follow-up have been described previously. All children in the current analysis had GHD, defined as a maximum stimulated GH level of <10 μg/L and no other cause for growth failure cited on their NCGS enrollment forms, and were being treated with rhGH.

Historical Perspective

Definitions of Adult Height

A wide variety of terms and definitions have been applied to the concept of adult height, including adult, mature, or final height, stature, results, or growth. To avoid confusion, we will use the term “adult height” for the historical data in the remainder of this review. Adult height has been defined most commonly as the stature attained by a person at an arbitrary age or growth velocity. Similarly, the adult heights of children with GHD have been defined as the stature achieved at various chronologic ages (CA),
bone age (BA), or growth velocities during or after GH treatment. The adult height in patients with GHD also has been defined simply as the height when GH therapy is discontinued.\textsuperscript{10,16,17} The National Cooperative Somatotropin Surveillance study, an ongoing survey of rhGH use in the treatment of adult GHD, defines adult height for its inclusion criteria as the stature of patients with fused epiphyses on hand and wrist radiographs. Terminology and definitions are presented in Table 1.

### Adult Heights in Untreated Growth Hormone Deficiency

Reliable data on the adult heights of persons with confirmed but untreated GHD are extremely rare. Historical, mythologic, and literary sources abound with stories of adults with severe short stature, but quantitative measurements and the causes of their short stature are usually unavailable. For example, Charles S. Stratton (Tom Thumb) and his wife, Lavinia Bump (Lavinia Warren), were reportedly sexually mature at adult heights of 96 and 81 cm, respectively. It has been speculated that one or both may have had GHD, but the exact cause of their short stature is not known.

Wit et al reviewed height data on 55 patients with untreated isolated GHD.\textsuperscript{19} The mean adult height of 22 boys and 14 girls who had undergone spontaneous puberty was −4.7 SDS (range, −6.1 to −3.9 SDS). These 36 consisted of 16 patients with a diagnosis of sexual ateliosis (clinical GHD plus spontaneous puberty) and 20 patients with a diagnosis of isolated GHD based on biochemical testing. The remaining 19 patients with GHD (all boys) were being treated with hydrocortisone and thyroxine plus sex steroids to induce puberty. Androgen therapy began at a mean age of 15.6 years, and their mean adult height was −3.1 SDS.

### Adult Heights in Children With GHD Treated With Pituitary GH (pitGH)

The clinical use of cadaver pitGH spanned nearly 30 years (mid-1950s to 1980s), but few, if any, patients were treated with continuous pitGH until their full adult height potential had been realized. The supplies of pitGH were limited, and treatment was provided at low, intermittent doses, with adjustments rarely made for changes in body size or weight. To be treated with pitGH, patients had to meet strict criteria for GHD, and treatment often was discontinued when predetermined heights were reached.\textsuperscript{2,16}

The National Pituitary Agency supervised the use of pitGH in the majority of patients with GHD in the United States from 1963 to 1985. Treatment initially was allowed for 8 months of each year (alternating 2 months on therapy and 1 month off) and was continued until both boys and girls had reached a final height of 152 cm (−3.8 SDS for boys and −2.0 SDS for girls). The height limitation was gradually increased to 168 cm for boys and 163 cm for girls.\textsuperscript{18} Other than these predetermined limits, no information is available on the adult heights in these patients: “Final height information was not sought for any of the projects, including the National Collaborative Project, sponsored by the National Pituitary Agency,” (S. Douglas Frasier, MD, personal communication, May 1998).

No national database was established for adult heights with pitGH treatment, but some limited reports do exist. For instance, in one of the first studies that included data on posttreatment heights, a group of 15 patients with GHD, 2 to 17 years of age, were given pitGH for 2 to 5 years. Treatment was discontinued after “acceptable adult stature” had been achieved in 4 boys at CAs ranging from 16.3 to 17.7 years, estimated heights from 137 to 164 cm (mean, 149 cm), and height SDS from −6 to −1 (mean, −3.6 SDS).\textsuperscript{16}

Wit et al summarized the effects of pitGH treatment on adult height in a total of 426 patients with GHD in several studies.\textsuperscript{19} A total of 236 of these patients (184 boys, 52 girls) underwent spontaneous puberty, and puberty was induced in 190 (139 boys, 51 girls). All patients had a mean peak stimulated GH level of <7.5 μg/L. The GH was given 2 to 4 times a week, at doses ranging from 4 to 20 IU per week to 0.1 to 0.5 IU/kg per week.

After pitGH treatment the mean adult height in those with spontaneous puberty was −2.3 SDS (range, −3.4 to −1.5 SDS) for boys and −3.5 SDS (range, −4.7 to −2.9 SDS) for girls. The mean adult heights in those with induced puberty was −1.4 SDS (range, −1.9 to −1.1 SDS) for boys and −1.5 SDS (range, −2.2 to −1.2 SDS) for girls. The mean adult height of all patients with spontaneous puberty was minus2.8 SDS (range, −4.7 to −1.5 SDS)\textsuperscript{10,20–22} and after induced puberty was −1.6 SDS (range, −2.4 to −1.1 SDS)\textsuperscript{10,23–24}

Other researchers have reported comparable differences between the adult heights in patients with isolated GHD and spontaneous puberty and the adult heights in those with GHD and induced puberty (multiple pituitary hormone defects). Bourguignon et al found mean adult heights after spontaneous puberty in 8 boys treated with pitGH of −2.5 SDS and after induced puberty in 14 boys of −1.8 SDS.\textsuperscript{11} Pierson et al reported the adult heights in 25 postpubertal adults with childhood GHD after the completion of pitGH treatment.\textsuperscript{12} Their mean CAs were 22.7 years (men) and 23.2 years (women). The mean adult height in 10 men with isolated GHD was 157.7 cm, in 7 men with multiple pituitary hormone defects was 163.3 cm, and in 8 women with GHD was 147.9 cm (approximately −2.9, −2.0, and −2.6 SDS, respectively).\textsuperscript{12}

### TABLE 1. Definitions of Adult Height

<table>
<thead>
<tr>
<th>Category</th>
<th>Terminology</th>
<th>Definition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH therapy discontinuation</td>
<td>Adult stature</td>
<td>“Acceptable adult stature”</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Final growth</td>
<td>“Patient satisfied with height and wished to stop GH”</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Height limitation</td>
<td>Pituitary GH provided until predetermined height reached</td>
<td>16</td>
</tr>
<tr>
<td>Age or maturity</td>
<td>Young adult</td>
<td>Height over age 20 years (men) or 18 years (women)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Adult stature</td>
<td>Height at age 18 years</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Mature height</td>
<td>“Maximum height attained and sustained during the subject’s third decade”</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Final results</td>
<td>Height when BA ≥15 years (boys) or ≥13 years (girls)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Parental height</td>
<td>Stature measured at nearest to 30 years of age</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Young adult</td>
<td>“One year after completion of pubertal development”</td>
<td>12</td>
</tr>
<tr>
<td>Growth velocity</td>
<td>Completed growth</td>
<td>Fused epiphysis</td>
<td>NCSS 1998</td>
</tr>
<tr>
<td></td>
<td>Adult height</td>
<td>&lt;1 cm/y</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Final growth</td>
<td>&lt;2 cm/y</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Final height</td>
<td>&lt;2 cm/6 mo</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Final height</td>
<td>&lt;2 cm/y</td>
<td>13</td>
</tr>
<tr>
<td>Combination</td>
<td>Final height</td>
<td>Growth rate &lt;1 cm/6 mo; BA 18 years (boys) or 17 years (girls)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Near-adult height</td>
<td>Growth rate ≥1 cm/6 mo; CA and BA ≥14 years (girls) and 16 years (boys)</td>
<td>14</td>
</tr>
</tbody>
</table>
Adult Heights in Children With GHD Treated With rhGH

Recombinant DNA technology has resulted in potentially unlimited supplies of GH, and the use of rhGH has consequently increased. The strict criteria for the diagnosis of GHD have lessened, interrupting therapy because of limited supplies is no longer necessary, and indications for rhGH therapy beyond pediatric GHD have been added (Turner syndrome, chronic renal insufficiency, adult GHD). However, long-term studies in pediatric patients with GHD who have been treated exclusively with larger, consistent doses of rhGH are few, and comparing and interpreting height measurements continue to be complicated by different treatment regimens and endpoints. The definitions of adult height in recent rhGH studies include the stature attained when the growth velocity was <2 cm per year,17 <1 cm per 6 months plus BA of 17 years (girls) or 18 years (boys),1 and 1 cm per 6 months plus both CA and BA of at least 14 years (girls) and 16 years (boys).14

The Kabi Pharmacia International Growth Study database was searched for rhGH-treated patients who met the criteria for adult height.19 Ninety-five patients (55 boys, 40 girls) were found, 72 of whom had spontaneous puberty and 23 induced puberty. The injection frequency varied from two or three injections per week to daily. Thirty-nine boys with GHD underwent spontaneous puberty at a mean CA of 13.8 years and height of −1.8 SDS; at adult height their mean CA was 17.4 years and height SDS was −1.3. Puberty was induced in 16 boys at an older mean CA (16.2 years) and height of −0.7 SDS; at adult height their mean CA was 19.3 years and height SDS was −0.2. Thirty-three girls with GHD underwent spontaneous puberty at a mean CA of 13.0 years and height of −1.7 SDS; at adult height their mean CA was 16.5 years and height SDS was −1.1. Puberty was induced in 7 girls at a mean CA of 14.4 years and height SDS of −0.5; at adult height their mean CA was 17.1 years and mean height SDS was −0.5. The mean adult height in all patients, regardless of their pubertal status, was −1.0 SDS for boys and −1.1 SDS for girls.

Near adult heights (NAH) after rhGH treatment have been reported in 121 patients with GHD (72 boys and 49 girls) in Genentech clinical trials.14 The dose of rhGH was 0.3 mg/kg per week, and the injection schedule ranged from three times a week to daily. The mean initial height in girls was −3.4 SDS, their height at the onset of puberty was −1.9 SDS, and their NAH after rhGH treatment was −0.7 SDS. In boys the mean initial height was −3.0 SDS, height at the onset of puberty was −1.9 SDS, and NAH was −0.7 SDS.

One more study that highlights the difficulties of assessing adult heights will be reviewed. Chipman et al11 reviewed data from 314 patients with GHD who had been treated with rhGH at 0.18 to 0.24 mg/kg per week, given three to six times per week. Adult height in these patients was defined as a growth velocity of <1 cm per 6 months plus BA of 17 years (girls) or 18 years (boys). Height measurements were obtained for two groups of patients: those who completed therapy and those who stopped it early.

Twenty-eight patients (8.9%) completed the rhGH treatment protocol according to their centers' criteria. Subsequent chart reviews, however, indicated that all 28 of these patients had BAs of <17 (or 18) years and only 9 had growth rates of <1 cm per 6 months. Treatment with rhGH was discontinued in 136 patients (43.3%) before the completion of growth; according to follow-up questionnaires, 13 of these 136 patients eventually met both the growth velocity and the BA criteria for adult height. The mean CAs in the protocol-complete group were 16.0 years (girls) and 16.8 years (boys) and in the early-discontinuation group were 19.1 years (women) and 19.3 years (men). The mean adult height SDS in females were −0.9 (protocol complete) and −1.1 (early discontinuation) and in males were −1.4 (complete) and −0.9 (early discontinuation).

In this retrospective analysis, no patients who completed rhGH therapy actually met the investigators' adult height criteria, and the reported adult heights were in reality "rhGH-completion" heights, with an unknown degree of growth potential remaining. Furthermore, the available data from a patient group that typically are not analyzed (those who discontinue therapy and the study protocols) suggest that additional growth may occur after GH therapy has been stopped. Another possibility is that after discontinuing the study protocol, some patients may have been treated with rhGH from another source.

The NCGS Perspective

Four different definitions of NAH were tested. In each case, patients who met the CA, BA, pubertal status, and/or growth-rate criteria for NAH were selected. This NAH was compared with the last measured height (obtained at least 6 months after the NAH).

The purpose of this was to determine how close a given definition of NAH was to being a "true" adult height.

The first definition of NAH selected was based on CA alone. For men it was a CA of at least 20 years and for women a CA of at least 18 years. By using this definition of NAH, 27% of the patients grew at least 9 cm in the 0.5 to 7.4 years after they had met the criteria for NAH. Adding the requirement that the patient also have Tanner stage 4 or greater pubertal development decreased the proportion of patients who grew at least 5 cm to 10%.

For this reason, we subsequently required pubertal development of Tanner stage 4 or greater in addition to the other criteria for NAH.

The third definition of NAH required that in addition to Tanner stage 4 or greater, both CA and BA be at least 16 years for boys and at least 14 years for girls. Subsequent growth is summarized in Fig 1. By using this definition, only ≤5% of the patients had subsequent growth of ≥5 cm after they had reached the defined NAH.

In the final definition tested, a growth rate of <2 cm/y was required in addition to the pubertal, CA, and BA criteria of the previous definition. By using this definition, only 1% of the patients grew ≥5 cm after having reached the defined NAH. Results from each analysis are summarized in Table 2.

DISCUSSION

Treating children who have GHD with GH results in an estimated mean height gain of 1.5 to 2.0 SDS.19 The adult height outcomes in these patients relative to the adult heights of the general population, however, often have been disappointing. In earlier studies ≥50% of patients with GHD did not attain posttreatment heights greater than the third percentile,1,14 presumably owing to limited availability of pitGH, low doses, and sporadic administration.1,13

There is now evidence that the current therapeutic regimens can improve on these results. Price et al13 reported an overall greater gain in the adult heights in children with GHD who were treated with rhGH. The positive correlates of adult height SDS included enrollment height SDS, duration of GH treatment, target height SDS, and injection schedule. However, the adult height SDS were greater in those with induced puberty than in those with spontaneous puberty.13 In contrast, using larger doses of rhGH (0.3 mg/kg/wk), Blethen et al11 reported that spontaneous puberty was not associated with smaller adult height SDS. In this study, the patients' height SDS
TABLE 2. Near-adult Height and Subsequent Growth in Patients in the NCGS

<table>
<thead>
<tr>
<th>Definition of NAH</th>
<th>No. of Patients (M/F)</th>
<th>Cause of GHD (O/I)</th>
<th>Years From NAH to LMH, Median (Range)</th>
<th>Growth After NAH, cm (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA ≥20 y (M), ≥18 y (F)</td>
<td>159 (69/90)</td>
<td>79/80</td>
<td>1.6 (0.5–7.4)</td>
<td>48 25 27</td>
</tr>
<tr>
<td>CA ≥20 y (M), ≥18 y (F); Tanner stage ≥4</td>
<td>49 (23/26)</td>
<td>17/32</td>
<td>1.3 (0.5–3.4)</td>
<td>74 16 10</td>
</tr>
<tr>
<td>BA and CA ≥16 y (M), ≥14 y (F); Tanner stage ≥4</td>
<td>483 (313/170)</td>
<td>127/356</td>
<td>1.0 (0.5–6.9)</td>
<td>53 42 5</td>
</tr>
<tr>
<td>GV &lt;2 cm/y; BA and CA ≥16 y (M), ≥14 y (F); Tanner stage ≥4</td>
<td>186 (101/85)</td>
<td>67/119</td>
<td>1.0 (0.5–6.3)</td>
<td>83 16 1</td>
</tr>
</tbody>
</table>

O indicates organic; I, idiopathic; LMH, last measured height; GV, growth velocity.

The values for years from NAH to LMH and for growth after NAH were similar between the subgroups M and F and between the subgroups O and I within each definition of NAH. Approximately 75% of these patients had discontinued NCGS by their LMH; the remaining 25% had not.

increased during puberty, and 106 (87.6%) of 121 patients reached an NAH within 2 SD of the mean for American adults. The positive correlates of height outcome included pretreatment predicted adult height SDS, duration of rhGH treatment, and first-year growth rate after the initiation of rhGH therapy. The apparent outcome of GH treatment (ie, “adult” or “final” height) depends not only on treatment factors (age at GH initiation, GH dose, continuity and duration of GH therapy), but also on the definition of adult height used. Applying an NAH definition based on CA alone can be adequate for some patients, but, as shown by the NCGS data, some patients older than 20 years continue to grow by ≥5 cm after their therapy has been stopped and their NAH established. Requiring late puberty as well as the CA criteria in the definition of NAH resulted in NAH values closer to the last measured heights. Requiring specified BA and CA criteria in addition to late puberty reduced further the number of patients who grew ≥5 cm. Adding a growth rate of <2 cm per year to the CA, BA, and late puberty criterion brought the NAH measurement even closer to the last measured height. Thus, in evaluating the height outcome with GH therapy in GHD, the more relevant information there is in the definition of NAH, the more likely it is that true adult height has been attained.

SUMMARY

The available data indicate that persons with GHD who are not treated with GH attain a mean adult height of −4.7 SDS (range, −6.1 to −3.9 SDS). Girls who are treated with pitGH attain an adult height in the range of −4.7 to −1.2 SDS, and those who are treated with larger doses of rhGH attain an adult height in the range of −1.4 to −0.5 SDS. Boys attain an adult height in the range of −3.6 to −1.1 SDS with pitGH and of −1.3 to −0.7 SDS with rhGH. Spontaneous puberty in children with GHD has often had a negative impact on the adult heights attained. The height gains in boys with spontaneous puberty after the initiation of GH therapy range from 0.9 to 2.3 SDS (mean, 1.8 SDS) and after induced puberty from 1.9 to 3.7 (mean, 3.1 SDS). The gains in girls are 1.3 to 2.1 SDS (mean, 1.8 SDS) with spontaneous puberty and 1.8 to 4.1 SDS (mean, 2.9 SDS) with induced puberty.

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REFERENCES

Issues in the Transition From Childhood to Adult Growth Hormone Therapy

David B. Allen, MD

ABSTRACT. The consequences of severe growth hormone deficiency (GHD) in adults and the beneficial effects of GH replacement therapy are clear. However, the majority of children who have a diagnosis of GHD and who are treated with GH do not have permanent GHD and will not require treatment during adulthood. Several issues must be considered in selecting candidates for adult GH treatment and transitioning their care from pediatrics to adult medicine. Counseling about possible lifelong treatment should focus on children with panhypopituitarism and those with severe isolated GHD that is associated with central nervous system abnormalities. When to terminate growth-promoting GH therapy should be guided by balancing the high cost of late-adolescent treatment with the attainment of reasonable statural goals. Retesting for GH secretion is appropriate for all candidates for adult GH therapy; the GH axis can be tested within weeks after the cessation of treatment, but confirming an emerging adult GHD state with body composition, blood lipid, and quality-of-life assessments may require 1 year or more of observation. Selecting patients for lifelong adult GH replacement therapy will present diagnostic, therapeutic, and ethical problems similar to those in treating childhood GHD. The experience and expertise of pediatric endocrinologists in diagnosing and treating GHD should be offered and used in identifying and transitioning appropriate patients to adult GH therapy. Pediatrics 1999;104:1004–1009; clonidine test, growth hormone deficiency, hypothalamic-pituitary region, insulin tolerance tests, multiple pituitary hormone deficiency.

ABBREVIATIONS. GHD, growth hormone deficiency; GH, growth hormone; IGHD, isolated GHD; MPHD, multiple pituitary hormone deficiencies; ITT, insulin tolerance test.

From the Department of Pediatric Endocrinology, University of Wisconsin Children’s Hospital, Madison, Wisconsin.

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Reprint requests to (D.B.A.) H4/448 CSC—Pediatrics, 600 Highland Ave, Madison, WI 53792. E-mail: ballen@facstaff.wisc.edu

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It is becoming increasingly clear that adults with growth hormone deficiency (GHD) have physiologic (eg, greater subcutaneous and visceral fat mass, subnormal muscle mass, lower bone mineral density, lower cardiac function, higher low-density lipoprotein cholesterol level) and functional (less physical performance, cognitive function, and sense of well-being) impairments that are at least partially reversed by GH replacement therapy. The prospect of lifelong treatment with GH for certain children with GHD is a significant departure from traditional GH therapy, which was confined to childhood and was dictated by statural goals. It also presents several new challenges in preparing, identifying, and transitioning appropriate patients from childhood to adult GH therapy.

In this article, I discuss five important issues in the transition from childhood to adult GH therapy: 1) Which children should and should not be counseled to expect adult treatment? 2) When is it appropriate to switch from higher-dose, higher-cost growth-promoting treatment to lower-dose adult treatment? 3) Should GH treatment be interrupted between childhood and adulthood and, if so, for how long? 4) How should the need for GH replacement therapy be assessed in young adult candidates? 5) What degree of advocacy is appropriate in counseling competent young adults with GHD who are reluctant to continue treatment?

PREPARING GH-TREATED CHILDREN

The value of GH treatment in children with severe GHD is now well established. If treated early and consistently, children affected reach an adult height within the normal range.1 The current clinical practice is to discontinue GH therapy when their linear growth is either complete or their height is in the normal range for adults, and most children who are treated with subcutaneous GH look forward to eventual freedom from daily injections. Because it is likely that some of these patients would benefit from treatment during adulthood, it is important to provide guidance about continued treatment.

Which children should be prepared for adult GH treatment? The answer is complicated by the fact that