A cardinal clinical feature of Turner syndrome (TS) is linear growth failure resulting in extreme short stature: the median adult height of untreated women with TS is 143 cm, 20 cm (8 in.) below that of the general female population. In the largest multicenter, randomized, long-term, dose-response study conducted in the United States, 232 subjects with TS received either 0.27 or 0.36 mg/kg-wk of recombinant human GH with either low dose ethinyl E2 or oral placebo. The study was placebo-controlled for both GH and estrogen for the first 18 months and remained placebo-controlled for estrogen for its duration. The near-final height of the 99 subjects whose bone age was at least 14 yr was 148.7 ± 6.1 cm after 5.5 ± 1.8 yr of GH started at a mean age of 10.9 ± 2.3 yr; this represents an average increase of 1.3 ± 0.6 SD scores from baseline (TS standard). Height was greater than 152.4 cm (60 in.) in 29% of subjects compared with the expected 5% of untreated patients. Mean near-final heights of subjects who received the lower GH dose, with or without estrogen, were 145.1 ± 5.4 and 149.9 ± 6.0 cm, respectively; those who received the higher GH dose with or without estrogen achieved mean near-final heights of 148.1 ± 6.0 and 150.4 ± 6.0 cm, respectively. Factors that most impacted outcome were younger age, lower bone age/chronological age ratio, lower body weight, and greater height SD score at study entry. This study demonstrates significant GH-induced improvement in height SD score, with correction of height to within the normal channels for a significant number of patients, and provides evidence of a GH dose-response effect. These data also indicate that early administration of estrogen, even at relatively low doses, does not improve gain in near-final height in patients with TS. (J Clin Endocrinol Metab 87: 2033–2041, 2002)
ing treatment arms. To achieve this goal, the starting dose of ethinyl E2 was based on subject age and weight at study entry. Subjects 8 to less than 10 yr of age with body weight (BW) greater than 20 kg received between 25–50 mg/kg/d ethinyl E2 depending on weight within the age category. Subjects in the 10 to less than 12 yr age group received between 67–100 mg/kg/d, and subjects in the over 12 yr age group received between 160–200 mg/kg-d ethinyl E2. Subjects less than 8 yr of age (n = 32) or less than 20 kg BW (n = 5) did not receive E2 at study entry, but began to receive E2 (randomized to an E2-receiving group) after 18 or 36 months in the study, once they had achieved adequate age and weight. Thus, the per kg E2 dose was greater with older baseline age, but remained lower than replacement doses throughout. After completion of the first 18 months of the study, subjects at least 13.5 yr of age could begin standard open-label sex steroid replacement at the discretion of the investigator.

After a blinded interim analysis the subjects receiving placebo injections and oral placebo were reassigned, without unblinding the treatment status to patients or investigators, to join the group receiving 0.36 mg/kg-wk GH with oral placebo for the second phase of the study from 18 months onward. For the purpose of the analysis of long-term data, therapy baseline for these subjects is the time at which they began GH, after completion of the placebo phase of the study. Subjects completed the study when HV was less than 2 cm/yr and BA was 15 yr or greater.

Efficacy and safety parameters

Subjects were assessed every 3 months for the first 6 yr of study, then every 6 months until study completion. Evaluations included height (the average of three measurements taken without shoes, using a stadiometer), weight, and pubertal status. Blood chemistry, hematology, hemoglobin A1c, and thyroid function tests (T4 and TSH) were performed at every visit. Fasting and 2-h postprandial glucose and insulin were measured every 6 months. IGF-I, GH antibodies, and Escherichia coli polypeptide antibody were measured every 3 months for the first 18 months, at 24 months, and then annually thereafter. Standard urinalysis (for protein, glucose, cells, etc.) was performed every 3 months for the first 24 months of study, then every 6 months thereafter. An x-ray of the left wrist and hand for BA was obtained every 6 months for 24 months, then annually thereafter. The films were read by a single observer who was blinded to treatment status.

Data analysis

Data obtained during the initial 18-month placebo-controlled phase of the study are reported for each of the five original randomization groups. Thereafter, because placebo subjects were transferred onto active therapy, data are reported for four active therapy groups: group 1) 0.27 mg/kg-wk GH with oral placebo; group 2) 0.27 mg/kg-wk GH with low dose estrogen; group 3) 0.36 mg/kg-wk GH with oral placebo; and group 4) 0.36 mg/kg-wk GH with low dose estrogen.

The analysis of near-final height included all girls whose BA was at least 18 months onward. For the purpose of the analysis of long-term data, the impact of GH dose was addressed by comparing change in height SD scores between subjects who received 0.27 mg/kg-wk GH and those who received 0.36 mg/kg-wk GH. Similarly, the effect of low dose estrogen was assessed by comparing change in height SD score between subjects who received low dose estrogen and those who received oral placebo. To address the issue of variability of response to therapy, a number of factors were evaluated, including baseline factors such as karyotype, age at initiation of therapy, BA/chronological age (CA) ratio, height and target height (midparental height), weight, body mass index, and therapy-related factors, such as GH dose, duration of GH therapy, and presence or absence of concomitant low dose estrogen. Exploratory analyses were performed to determine the potential impact of these factors on near-final height.

Statistical methods

The SAS software system (version 6.12, SAS Institute, Inc., Cary, NC) was used to perform statistical analyses. A two-sided P value of 0.05 was considered statistically significant for all tests. Tests of baseline characteristics for the intent to treat population were performed using one-way ANOVA for numeric variables and χ² or Fisher’s exact tests for categorical variables.

Where least squares means (and inferences) are reported, these are based on a statistical model (analysis of covariance; ANCOVA) that included baseline age, baseline height SD score (NCHS), and baseline height SD score [TS standard (8)], study site (pooled when numbers small), baseline age stratum, estrogen (low dose or placebo), and GH (0.27 or 0.36 mg/kg-wk). Potential influences on therapy outcome were explored by stepwise regression and backward elimination models.

Results

Baseline data

Of 232 subjects enrolled in the study, 224 received GH therapy for at least 180 d and are considered acceptable for evaluation of efficacy (intent to treat group). Study entry data for these subjects were not significantly different between treatment groups (Table 1). As reported in other studies, the majority of subjects had classic 45,X monosomy (67.4%), whereas 20% of subjects had various mosaic karyotypes (Table 2).

Growth during the placebo-controlled phase of study

This study provides the longest reported period of placebo-controlled data for GH treatment in TS. There was no significant difference among the five treatment groups for pretreatment HV or baseline height (Table 1). All four GH-

<table>
<thead>
<tr>
<th>TABLE 1. Baseline data for patients who received at least 180 d study drug</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>BA (yr)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Height SD score (NCHS)</td>
</tr>
<tr>
<td>Height SD score (Lyon)</td>
</tr>
<tr>
<td>Midparental height (cm)</td>
</tr>
<tr>
<td>Midparental height SD score</td>
</tr>
<tr>
<td>Pre-study HV (cm/yr)</td>
</tr>
</tbody>
</table>

Data shown are mean ± 1 SD. Lyon, Lyon TS growth data (6). At 18 months of study, the group receiving placebo injections and placebo oral tablets crossed over (blinded) to join the group receiving 0.36 mg/kg-wk GH and oral placebo.
treated groups showed a sharp and significant increase in HV compared with pretreatment values (Fig. 1). HV declined slightly in all GH-treated groups after the initial peak, but was significantly greater than that in the placebo group throughout the 18-month placebo-controlled period (HV 0–18 months: GH 0.27/pla, 6.6 ± 1.1 cm/yr; GH 0.27/LDE, 7.0 ± 1.4; GH 0.36/pla, 6.8 ± 1.1; GH 0.36/LDE, 7.0 ± 1.2; Pla/Pla, 4.2 ± 1.1; P < 0.001). There were no significant differences in HV between GH dose groups or between groups receiving low dose E2 vs. oral placebo.

Near-final height

The study was closed in 1996 in preparation for data analysis for FDA submission to support the approval of GH for patients with TS. At the time of study closure and subsequent data analysis 52 subjects had formally completed the study and an additional 47 subjects had achieved a BA of at least 14 yr. Thus, 99 subjects whose BA was at least 14 yr at the last available measurement were evaluated for near-final height (Table 3). The mean age at the start of active therapy for this group of 99 subjects was 10.9 ± 2.3 yr. However, the subjects

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>n (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45,X</td>
<td>151 (67.4%)</td>
</tr>
<tr>
<td>45,X/46,XXqiq</td>
<td>19 (8.5%)</td>
</tr>
<tr>
<td>45,X/46,XXr</td>
<td>10 (4.5%)</td>
</tr>
<tr>
<td>45,X/46,XX</td>
<td>9 (4.0%)</td>
</tr>
<tr>
<td>46,XXqiq</td>
<td>9 (4.0%)</td>
</tr>
<tr>
<td>45,X/47,XXX</td>
<td>3 (1.3%)</td>
</tr>
<tr>
<td>46,XXp</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>45,X/46,XXp</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>45,X/46,XX/47,XXX</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (8.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>224</td>
</tr>
</tbody>
</table>

Subjects with Y component in karyotype were excluded from study. Chi-square analysis showed no significant difference between treatment groups for proportions of subjects with 45,X vs. other karyotypes.

FIG. 1. HV during the 18-month placebo-controlled phase of study, calculated on 6-month measurements. Subjects in each of the GH-treated groups showed marked increase in HV compared with pretreatment and grew significantly faster than the placebo group throughout (P < 0.001). Pla/Pla, Placebo injections with oral placebo (n = 41); GH 0.27/pla, 0.27 mg/kg-wk GH with oral placebo (n = 45); GH 0.27/LDE, 0.27 mg/kg- wk GH with low dose estrogen (n = 47); GH 0.36/pla, 0.36 mg/kg- wk GH with oral placebo (n = 49); GH 0.36/LDE, 0.36 mg/kg- wk GH with low dose estrogen (n = 42).

TABLE 3. Summary data for subjects with bone age ≥14 yr at last observation

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>BA (yr)</th>
<th>Height (cm)</th>
<th>Change 1 SD</th>
<th>Pre-study HV (cm/yr)</th>
<th>Change 1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH 0.27/pla (n = 15)</td>
<td>10.6 ± 1.9</td>
<td>16.8 ± 1.4</td>
<td>104 ± 23</td>
<td>11.2 ± 2.2</td>
<td>18.7 ± 1.5</td>
</tr>
<tr>
<td>GH 0.27/LDE (n = 15)</td>
<td>8.6 ± 1.3</td>
<td>15.1 ± 1.0</td>
<td>87 ± 22</td>
<td>9.2 ± 2.2</td>
<td>14.8 ± 0.7</td>
</tr>
<tr>
<td>GH 0.36/pla (n = 49)</td>
<td>6.2 ± 1.2</td>
<td>15.5 ± 1.5</td>
<td>62 ± 22</td>
<td>7.0 ± 2.2</td>
<td>16.7 ± 1.2</td>
</tr>
<tr>
<td>GH 0.36/LDE (n = 42)</td>
<td>4.7 ± 1.1</td>
<td>14.9 ± 1.0</td>
<td>42 ± 22</td>
<td>5.5 ± 2.4</td>
<td>14.9 ± 1.0</td>
</tr>
</tbody>
</table>

Data shown are mean ± 1 SD. Lyon, Lyon TS growth data (6).
(n = 19) who were initially in the placebo group began active therapy about 1.5 yr later than the remainder of the group (12.0 ± 2.0 vs. 10.7 ± 2.3 yr). At a mean CA of 16.4 ± 1.4 yr, after 5.5 ± 1.8 yr of active therapy, the average height for the whole group was 148.7 ± 6.1 cm (−2.2 ± 1.0 sd score by NCHS standards, +1.5 ± 1.0 sd score by TS standards). This represents a mean increase of 1.3 ± 0.6 sd score from baseline by TS standards. For 80% of subjects (79 of 99), near-final height was above the median (50th percentile) height for untreated adult women with TS of 143 cm (8). In addition, height was greater than 152.4 cm (60 in.) for 29% of subjects (29 of 99) compared with the expected 5% of untreated subjects. There was no difference in mean near-final height between the subset of 52 subjects who fulfilled criteria for protocol completion (BA, ≥15 yr; HV, <2.0 cm/yr) and are considered the most mature and the larger group of 99 subjects.

To evaluate the growth response in the subject population as a whole, the intent to treat group (all subjects who received at least 180 d of active therapy; n = 224) was also evaluated at the last available height measurement for the study. After 4.9 ± 2.4 yr of GH therapy, at a mean CA of 14.9 ± 2.6 yr, the average height was 143.3 ± 11.6 cm. This represented an average 1.3 ± 0.7 increase in height sd score (TS standard) over baseline. Notably, the mean BA of this group at the last available measurement was only 13.1 ± 2.4 yr, indicating significant remaining growth potential. In fact, based on this BA and height, the predicted mature height of the study subjects as a whole would be almost identical to that of our primary analysis group. This finding indicates that the mature subjects with BA of 14 yr or more provide a fair representation of the complete study population. The individual subject data at baseline and last available height are summarized in Fig. 2.

**Effect of GH dose**

The average near-final heights of the subjects who received 0.27 mg/kg-wk GH were 145.1 ± 5.4 and 149.9 ± 6.0 cm, for the estrogen-treated (n = 24) and placebo (n = 15) subgroups, respectively. For those who received 0.36 mg/kg-wk GH, average near-final heights were 149.1 ± 6.0 and 150.4 ± 6.0 cm for the estrogen-treated (n = 22) and placebo (n = 38) subgroups, respectively. In addition to the finding of greater absolute height for those who received 0.36 mg/kg-wk, subjects who received the higher GH dose had a significantly greater change in height sd score (NCHS standard) than those who received 0.27 mg/kg-wk [1.0 ± 0.1 vs. 0.6 ± 0.1 sd score (ANCOVA model; least squares mean ± se); P = 0.023]. Findings were similar when the data were analyzed using TS standards. Evaluation of change in individual subjects’ height sd score supports the grouped data and is shown in Fig. 3. As evidenced by the slope of the sd score lines, the majority of subjects in both GH dose groups showed substantial improvement in height sd score during the therapy period; however, those in the higher dose group tended to have greater slope of the sd score lines.

**Effect of early low dose ethinyl E2**

For the 99 subjects whose BA was 14 yr or more at the last available measurement, inclusion of early low dose ethinyl E2 in the regimen (n = 46) was associated with slight reductions in both the actual near-final height (centimeters) and the gain in height sd score (NCHS standard), although this effect was not statistically significant [0.7 ± 0.1 vs. 0.9 ± 0.1 sd score (least squares mean ± se); GH/estrogen-treated vs. GH/placebo-treated subjects; P = 0.11]. The lowest gain in height sd score was observed in the subjects who received 0.27 mg/kg-wk GH with concomitant estrogen, and the greatest gain was observed in the group that received 0.36 mg/kg-wk GH without estrogen [0.6 ± 1.0 vs. 1.1 ± 0.9 sd score (NCHS standard)].

GH- or estrogen-induced changes in the rate of skeletal maturation represent an important potential influence on the outcome of growth-promoting therapies in subjects with TS. BA x-rays were performed every 6 months for the first 2 yr of the study, then annually until study completion. The effects of the various therapies on skeletal maturation were analyzed by examining the changes in the ratio of BA to CA.
(BA/CA) across the study. Subjects who received GH (regardless of dose) with oral placebo had no significant change in BA/CA from baseline to end point. In contrast, those who received early low dose estrogen in conjunction with GH had a significant increase in BA/CA of $0.13 \pm 0.02$ (least squares mean ± SE; $P = 0.008$). As there was a lower gain in height $SD$ score and a significantly greater increase in BA/CA ratio in the early estrogen-treated subjects, it appears that the effect of early low dose estrogen on height gain was not favorable.

**Factors influencing response to therapy**

Variability in the magnitude of response to GH of individuals with TS has long been recognized, and the concept of certain patients being nonresponders to GH therapy has arisen, perhaps erroneously. A number of factors may potentially contribute to this variability, including pretreatment features such as karyotype, age at initiation of therapy, baseline height, and target height and therapeutic factors such as dose and duration of GH therapy and/or dose and timing of concomitant medications. These potential influences on therapy outcome were explored by stepwise regression and backward elimination models. The baseline factors found to contribute most significantly to the variance in response to GH (defined by change in height $SD$ score across the study) were age at start of GH therapy (younger subjects had greater increase in height $SD$ score), BA/CA ratio (lower BA/CA for a given age was associated with greater response), height $SD$ score (greater baseline height $SD$ score was associated with better outcome), and weight (lower baseline weight was associated with greater increase in height $SD$ score; $P < 0.05$ for each variable in the final model). The strong relationship between baseline age and change in height $SD$ score is shown in Fig. 4. In addition, the gain in height $SD$ score appeared normally distributed, as shown in Fig. 5. Eighty-seven of 99 subjects (88%) gained at least 0.5 $SD$ score in height. A small number of subjects showed negligible response to therapy (arbitrarily defined as $<0.3$ $SD$ score height increase across the duration of the study), 4 of 39 subjects who received 0.27
mg/kg·wk GH and 2 of 60 subjects who received 0.36 mg/kg·wk GH. These girls were older than the average starting age for the group as a whole (11.9–14.5 yr), and 4 of 6 had low midparental height (<158 cm, vs. 163 cm for the group overall), suggesting the possible influence of other stature-limiting genetic factors. In addition, the potential influence of noncompliance with therapy cannot be excluded. Only a single subject did not achieve any gain in height SD score.

**Safety**

Overall there were no major safety concerns during this study, and therapy was well tolerated. Conditions of particular relevance to TS, such as edema, hypothyroidism, and cardiovascular disorder, occurred rarely, with equal frequency in GH- and placebo-treated groups. During the placebo-controlled phase, otitis media occurred or worsened in a significantly greater number of subjects receiving GH than those receiving placebo [54 of 186 (29%) vs. 6 of 46 (13%); \( P = 0.037 \)]. However, the more general conditions, ear pain and ear disorder, were not different in frequency between groups, so the clinical significance of the higher reported occurrence of otitis media in GH-treated subjects is unclear. For the study as a whole, Otitis media was reported in 41% of subjects overall, ear pain in 27%, and hypothyroidism in 16%, whereas edema was reported in only 3%. There were no disorders that occurred significantly more frequently in subjects receiving the higher GH dose.

One subject who received 0.36 mg/kg·wk GH with low dose estrogen developed type 1 diabetes mellitus; however, there were no overall changes in carbohydrate tolerance or insulin sensitivity among the treatment groups (9). IGF-I concentrations were in the lower half of the normal range for age at baseline and remained within 2 SD of the mean during GH therapy in all but two subjects (data not shown).

Although the estrogen doses used in this study were intended to be growth promoting, rather than feminizing, a number of events, probably related to estrogen effect, were reported more frequently in subjects receiving low dose estrogen than in those receiving oral placebo. These events included breast pain, soreness, or tenderness in 10 girls who were in Tanner stages 1–3 of puberty (LDE, \( n = 7 \); Pla, \( n = 3 \)), and vaginal spotting or bleeding, or menarche, in 24 girls, 21 of whom were at Tanner stage 3 or beyond. Ten subjects, including 5 who had been in 1 of the placebo arms, were in the open label phase of the study in which standard estrogen replacement therapy was allowed. The other 14 were receiving low dose estrogen within the blinded phase of the study. Two subjects receiving LDE were reported to have heavy vaginal bleeding or metrorrhagia. Back pain was also reported more frequently in girls receiving LDE than in those receiving placebo [16 of 91 (18%) vs. 11 of 141 (8%); \( P = 0.035 \)].

Serious adverse events (defined as death, life-threatening, cancer, hospitalization, permanently disabling, drug overdose, or resulting in congenital anomaly in an offspring) were reported for 47 of 232 subjects. The majority (31 of 47) of these subjects were hospitalized for surgical procedures, either for elective management of conditions associated with TS (e.g. repair of coarctation) or related to accidental injury. Eleven subjects were hospitalized for various other reasons (infectious illnesses/dehydration, \( n = 5 \); psychosis, \( n = 1 \); abnormal liver function tests, \( n = 1 \); vaginal bleeding, \( n = 1 \); hematuria, \( n = 1 \); cardiac failure, \( n = 1 \); hypertension, \( n = 1 \)), and the remaining 5 subjects were reported to have accidentally overdosed on the study drug without significant consequence. Adverse events that were considered unexpected and possibly related to study drug were reported for 5 of 232 subjects (2%). These events comprised 2 cases of hypertension (in 1 subject this had been present for 11 yr), 2 surgical procedures (osteotomy/bunionectomy and repair of aortic aneurysm), and 1 case of scoliosis. There were no deaths and no reports of cancer or neoplasia during this study.

**Discussion**

The marked short stature of individuals with TS has been a therapeutic dilemma for over 60 yr. Henry Turner himself attempted to use pituitary extract to treat subjects with TS, but because of his disappointment with the results soon discontinued this practice (10). The effect of GH therapy in subjects with TS can be evaluated from two perspectives: the impact on childhood growth and the improvement in adult height. This study and others have demonstrated significant improvements in HV in response to GH therapy (11–14). The present study represents the largest and longest placebo-controlled analysis of GH effect on height velocity. A prior placebo-controlled study of human pituitary-derived GH demonstrated significantly greater height velocity SD scores in GH-treated subjects compared with placebo-treated subjects (15). However, this study was aborted after less than 6 months when pituitary-derived GH was withdrawn for safety reasons. In the present study GH-treated girls grew significantly faster than placebo-treated girls throughout the 18-month placebo-controlled period. In addition, GH-treated subjects grew, on the average, 73% faster than their pretreatment growth rate, resulting in significant catch-up toward peers, evidenced by an average 0.4 SD score improvement in height relative to NCHS standards during the initial 18-month study period. Although the socialization problems characteristic of girls with TS are multifactorial, partial normalization of stature in childhood may potentially help to defray some of these difficulties (16).

A number of studies have followed GH-treated subjects with TS to near-final height. Although the data are variable, the outcome has generally been positive. In the present study the mean height of the 99 subjects whose BA was at least 14 yr was 148.7 ± 6.1 cm, 5.7 cm greater than the median adult height of untreated women with TS of 143 cm (8). For almost one third of these young women, the impact of therapy was quite substantial, as 29 of 99 (29%) achieved a height greater than 152.4 cm or 5 ft, often considered a psychological and functional goal. In the study reported by Rosenfeld et al. (17) the mean adult height of the 17 subjects who received GH alone (0.375 mg/kg·wk) was 150.4 ± 5.5 cm. Our subgroup of subjects (\( n = 38 \)) whose therapy most closely matched that of the above study (0.36 mg/kg·wk GH with oral placebo), achieved an almost identical average near-final height of 150.4 ± 6.0 cm. Other studies have demonstrated quite disparate gains in adult or final height, ranging from less than
1 cm (18) to over 10 cm (19) or even complete normalization of height (20). The basis for these divergent results is multifactorial, and direct comparison of outcome across different studies is problematic. Study design varies widely with respect to age at initiation of therapy, dose and duration of GH, and use and timing of concomitant estrogens or anabolic steroids. In addition, methods for determining the impact of therapy, by comparison of attained height with predicted or projected heights vs. randomized or historical controls, can substantially affect the outcome data. Despite these discrepancies, most studies have demonstrated increased adult height with GH treatment in TS. Nevertheless, GH therapy in most of the regimens employed to date has been only partially effective, as most studies report adult heights at least 10 cm below the mean for women in the general population, indicating that only about 50% of the deficit has been corrected (17, 21, 22). However, this residual deficit appears likely to be amenable to optimization of the GH therapy regimen: younger age at therapy initiation, longer duration of therapy, and greater GH dose may improve outcome. The patients reported by Sas et al. (23) demonstrated dramatic increases in height sd score, and 85% achieved final heights in the normal range for the Dutch reference population. There was a dose-dependent impact of therapy; those patients who received an incremental regimen using approximately 0.045 mg/kg/d (0.32 mg/kg/wk) for the first year, 0.0675 mg/kg/d (0.47 mg/kg/wk) for the second yr, and 0.09 mg/kg/d (0.63 mg/kg/wk) thereafter achieved the greatest final height. The present study also evaluated the dose-response relationship to GH. The lower GH dose of 0.27 mg/kg/wk was similar to the GH dose used in the treatment of childhood GH deficiency (0.18–0.3 mg/kg/wk), whereas the higher dose of 0.36 mg/kg/wk (30% greater than the lower dose) was similar to the dose of 0.375 mg/kg/wk used in the other long-term United States study of GH therapy in TS (17). By ANCOVA the higher GH dose of 0.36 mg/kg/wk promoted a significantly greater increase in height sd score, indicating a clear dose-response effect. Other factors that significantly influenced the outcome were younger age, lower BA/CA ratio, lower BW, and greater height sd score at therapy start. Contrary to some reports, our study provides no evidence of a nonresponder subgroup of patients. Rather, the response in terms of gain in height sd score was normally distributed, with 88% of subjects gaining at least 0.5 sd score in height, and 68% gaining 1 sd score or greater.

Estrogen has a biphasic effect on linear growth: stimulatory at low doses (5–7, 24, 25) and inhibitory at high doses (26). This study sought to improve the growth response to GH therapy by early addition of ethinyl E2 at doses considered to be on the stimulatory part of the estrogen growth-response curve. Low doses of estrogen were initiated as early as 8 yr of age and continued until the onset of feminizing therapy, which was allowed from 13.5 yr onward. By ANCOVA, the mean gain in height sd score (by NCHS standard) for the 46 subjects who received early estrogen in conjunction with GH was 0.7, whereas that of the 53 subjects who received GH with oral placebo was 0.9. Although not statistically significant ($P = 0.11$) this finding combined with the increase in BA/CA ratio in the estrogen-treated subjects indicate that early low dose estrogen as administered in this study slightly reduced final height. However, the impact of estrogen on height gain ($–0.2$ sd score) was not as great as has been suggested in other studies. Although it is not surprising that physiological estrogen replacement at the normal time for puberty could limit height gain (19), this appears to be the case even with estrogen doses as low as 50 ng/kg-d (22). In conclusion, early initiation of estrogen at the doses used in this study provided no added height benefit. Furthermore, when used in conjunction with a lower GH dose, early E2 was associated with somewhat reduced final height gain, although the difference between mean final heights of the estrogen- and placebo-treated subgroups was not statistically significant. It is likely that the estrogen doses used in this study, although considered relatively low at the time the study was designed, were nevertheless higher than required for pure stimulation of linear growth, independent of skeletal maturation. Indeed, there is preliminary evidence that even lower doses of estrogen administered systemically may achieve the synergy with GH sought in this study (27). Although the present study does not demonstrate any height advantage associated with early estrogen administration, it should be noted that early low dose estrogen may provide other health benefits not addressed in this study. Such benefits may include improvement in neurocognitive function, memory, behavior, and self-concept (28–30), which may have significant impact on quality of life for these patients. Consequently, it will be important to study further the optimal dose and timing of estrogen replacement in these patients.

One of the key factors associated with significant improvement in final or adult height in TS is age at initiation of GH therapy. In many studies performed to date, including the present study, the average age at initiation of GH therapy has generally been in the vicinity of 11 yr. There are four primary consequences of such late initiation of therapy. First, the patient spends most of her childhood as a short child, often being related to as younger than age by teachers and peers. Second, because height deviates progressively away from the normal channels, the older the patient is at the start of therapy, the greater the deficit to be bridged, and the shorter the available time for therapy, the less likely it is that the individual will achieve a normal height. Third, in an effort to prolong the GH treatment period and maximize height gain, there is a tendency to postpone initiation of estrogen replacement therapy, potentially imposing further medical and psychosocial stress upon patients who already have a heavy burden of problems. Thus, it would seem logical to initiate GH therapy as early as possible to prevent progressive deterioration in height and to maximize the available preestrogen therapy period. In addition, early institution of GH should allow a more age-appropriate initiation of estrogen replacement therapy without loss of height potential (20, 22, 23, 31, 32).

In conclusion, this study demonstrates the positive effect of GH on near-final height in TS, with greater improvement at the higher GH dose and a trend toward lower final height in association with early low dose estrogen therapy. Despite the positive outcome of this study, the growth deficit of these patients was only partially corrected. As age at initiation of GH was a strong predictor for overall height gain in this
study, earlier initiation of therapy will probably improve final height outcome and allow for a more age-appropriate initiation of estrogen replacement without compromising adult stature.

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