

have constitutional delay of growth and maturation and can be expected to attain normal adult heights, even in the absence of therapy. Furthermore, the limitations in our ability to accurately diagnose GHD in children, as discussed above, may make it difficult to distinguish between some patients with ISS and others with partial GHD. There are some children who have been diagnosed as GHD who are in fact endocrinologically normal, just as there are some children categorized as having ISS who have either partial GHD or IGF deficiency. An additional concern with GH treatment of ISS is the issue of whether GH therapy results in an earlier onset of puberty than might have otherwise occurred, resulting in early epiphyseal fusion and the forfeiture of whatever height gain might have been attained during the early years of GH treatment.<sup>20</sup> These issues make it difficult to strongly recommend GH treatment for patients in these categories. On the other hand, there are undoubtedly ISS or IUGR patients who respond effectively to GH treatment, sometimes in as robust a manner as GHD patients. Accordingly, it is recommended that such patients be treated as part of prospective clinical trials or on a case-by-case basis, following a full discussion of the potential benefits and risks of therapy.

## THE FUTURE OF GH THERAPY

It is anticipated that GH will remain the treatment of choice for children with classic GHD, at least for the near future. Improved formulations, easier methods of reformulation and routes of administration, and long-lasting GH preparations should all enhance compliance with and, ultimately, the success of GH treatment. As more data are accumulated on the cost:benefit ratio of higher GH doses and as more experience is gathered on the adverse effects of high GH doses, a

better rationale for dosing should be developed. Therapy for non-GHD short children, such as those with CRI or TS, will continue to entail pharmacologic doses of GH to obtain short-term increases in height. Ultimate adult heights will be increased in TS patients, but whether the same will apply to patients with CRI or those with ISS and other causes of short stature remains to be determined. It is incumbent upon the endocrine community, pediatricians, and internists to continue careful monitoring of GH recipients for both short-term and long-term side effects. As experience accumulates with GHRH and other GH secretagogues, such as the GHRPs, we will be able to determine whether such therapeutic options provide any benefits over GH, even if only to a subset of patients.

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# How Safe and Effective Is Human Growth Hormone at Pharmacologic Dosing?

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Until 1985, cadaveric growth hormone (GH) was the sole source of human GH (hGH). The recommended dosage of between 0.24 and 0.3 IU/kg/wk or approximately 0.1 mg/kg/wk represented a compromise between the limited hormone supply and obtaining an optimal growth response. Since the introduction of biosynthetic hGH, the recommended dosage has increased to 0.3 mg/kg/wk (0.78 to 0.9 IU/kg/wk). This is roughly triple that used in the past and about 3 times the rate of endogenous GH production, except at ado-

lescence.<sup>1</sup> Use of this dose has led to growth acceleration in conditions in which GH may be partially deficient, namely idiopathic short stature,<sup>2</sup> as well as conditions in which GH secretion is normal, such as Turner syndrome,<sup>3</sup> bone dystrophies,<sup>4</sup> and intrauterine growth retardation.<sup>5</sup> Irrespective of their endogenous GH status, many short children will experience growth acceleration on currently recommended hGH doses. It is not surprising, therefore, that conditions other than classic (severe) GH deficiency (GHD) now account for more than 40% of patients treated in this country with biosynthetic hGH.

It is clear from these studies, however, that currently recommended doses of hGH often have gone beyond providing physiologic replacement and are now phar-

macologic. In Turner and other syndromes, for example, GH treatment is clearly aimed at producing a supraphysiologic effect, namely, a final height beyond that dictated by genetic potential.<sup>3</sup> This is a unique venture. Never before in the history of medicine has a biologic agent been used in an attempt to produce such widespread and permanent physical changes. However, to anticipate that this can be achieved without undesirable side effects also would be unprecedented. With this in mind, issues of safety should be of paramount concern. Unfortunately, there is a limit to which the available data from long-term replacement dosing or short-term pharmacologic dosing can be used to guarantee the ultimate safety of pharmacologic GH therapy.

There is a general consensus that over the short term pharmacologic GH dosing is reasonably safe.<sup>6</sup> An increased risk of intracranial hypertension and slipped capital femoral epiphysis has been documented, but the incidence of these complications is not large.<sup>6</sup> Of all potential complications, however, it is the risk of malignancy that should be of greatest concern. To date, 44 patients have developed leukemia following GH treatment, 12 of them from Japan.<sup>6</sup> The malignancies reported have been stem cell malignancies, such as leukemias, lymphomas, or thymomas.<sup>7</sup> Many of the patients had received pituitary-derived GH at moderate doses, and some had been off thera-

py for several years at the time of diagnosis. Of the 12 cases from Japan, 8 had idiopathic GHD and none of the usual risk factors for leukemia such as chemotherapy, radiation therapy, or preexisting malignancy. The data from Japan, therefore, remain unexplained.<sup>8</sup> It is generally agreed that there is insufficient evidence to incriminate GH therapy as a cause of leukemia, leukemic relapse, or tumor recurrence.<sup>6</sup> Nevertheless, a high index of suspicion needs to be maintained, since GH has the potential for being carcinogenic.<sup>7</sup> Acromegalic patients are at increased risk for developing benign and malignant tumors, particularly colon polyps and adenocarcinoma.<sup>9</sup> In a small group of acromegalic patients with active disease, 53% had colonic polyps.<sup>10</sup> In rats, both hypophysectomy and large doses of GH influence the effect of carcinogens.<sup>7</sup> Intraperitoneal injection of large doses of purified pituitary-derived GH into rats for up to 485 days resulted in rapid growth as well as neoplasia in multiple organs: lymphosarcomas of the lung, adrenocortical and adrenomedullary carcinomas, solid ovarian tumors, and breast tumors.<sup>7</sup> Such toxicology studies may have little relevance when considering physiologic replacement dosing, but the situation may be otherwise for pharmacologic dosing.

Of possible relevance to this issue are observations that melanocytic nevi of children with hypopituitarism and Turner syndrome show increased growth, increased proliferative activity, and atypical signs of differentiation during GH therapy, although there is no evidence of neoplasia.<sup>11,12</sup> Increased chromosome fragility also has been demonstrated in lymphocytes obtained 3 to 12 months into the treatment of normal short children, in addition to an increase in spontaneous chromosome rearrangements and a significant increase in bleomycin-induced aberrations.<sup>13</sup>

Hyperinsulinemia and insulin resistance have been noted in Turner syndrome and normal short children during GH therapy.<sup>14,15</sup> The absence of diabetes in all but a few patients in no way excludes the possibility of sequelae from a childhood spent in a state of hyperinsulinemia and insulin resistance.<sup>7,14</sup> Doubtless, most children will suffer no long-term effects, but this may not be the case for patients who already have a predisposition to atherosclerosis, diabetes, or hypertension. We have to admit that our knowledge of the natural history of these diseases is limited, and it may be decades before we can say with certainty that treatment has no influence on the development of these conditions.

Between 53% and 76% of patients with acromegaly develop joint problems, with a delay of approximately 10 years between the onset of acromegaly and the appearance of arthropathy.<sup>16</sup> Typical joint changes include widening of the joint spaces, osteophyte formation, joint capsule calcification, and mineralization of ligamentous insertions.<sup>17</sup> These changes are irreversible. Whether joint disorganization also occurs in developing joints as a consequence of higher-dose GH therapy will not be known for years. Reports of

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The *GGH* Editorial Board is pleased to announce Category 1 credit for *GROWTH, Genetics, & Hormones* from the University of Virginia School of Medicine. This enduring material has been planned and produced in accordance with the ACCME Essentials.

**Overview:** This enduring material is designed to provide physicians and other health professionals with current research and clinical information essential to providing quality patient care to children with growth problems and genetic disorders.

**Target Audience:** This enduring material is designed for pediatricians, pediatric endocrinologists, pediatric geneticists, and family medicine physicians interested in pediatric growth, genetics, and endocrine issues.

**Method of Physician Participation:** Physicians can study each issue of *GROWTH, Genetics, & Hormones*, respond to the post-test self-evaluation questions, and request CME credit for each issue. The estimated length of time to complete this enduring material is 1 hour.

**Learning Objectives:** Through participation in this enduring materials series, the participant will have the opportunity to:

1. Apply current research and advances to the management of patient care for optimum clinical outcomes.
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3. Conceptualize areas for future research in the field of growth and genetics.

avascular necrosis of the femoral head and slipped capital femoral epiphyses in a few treated children may or may not be the tip of the iceberg.<sup>18</sup> The potential for joint disturbances following high-dose GH treatment could be a particular concern in conditions with preexisting abnormalities of the growth cartilage. Modest short-term growth acceleration has been achieved in some patients with achondroplasia using pharmacologic GH dosing.<sup>4</sup> The basic defect in this condition is in the fibroblast growth factor receptor 3 gene and relates in some manner to abnormal cartilage growth and endochondral ossification. A bone dysplasia also contributes to the short stature of Turner syndrome, and an abnormality of cartilage cannot be excluded.<sup>19,20</sup> GH-treated children with chronic renal failure could be another group at high risk for bone and joint complications.<sup>18</sup> The extent to which abnormal joints and bones can be increased beyond their genetic potential and yet retain complete functional integrity throughout adulthood is not known.

Even if we follow a safety-first approach to pharmacologic GH treatment, the benefits of therapy are another important issue. We should not be placing any child at *unnecessary* risk. While higher-dose GH has improved the height prognosis for children with classic (severe) GHD, the situation is far more ambiguous with respect to children with other forms of GH insufficiency. This is a relevant concern, since these children now constitute a large proportion of children being treated with GH.

Neurosecretory GH dysfunction was first observed in children who had undergone prophylactic cranial irradiation for leukemia. Frequent sampling of endogenous GH over 24 hours demonstrated diminished GH secretion; GH pulses were attenuated in size and diminished in number.<sup>21</sup> Similar secretory patterns were subsequently found in other short, poorly growing children who had not undergone cranial irradiation and who had "passed" provocative GH stimulation testing.<sup>22</sup> The concept arose of a spectrum of GH insufficiency, ranging from short but normally growing children at one end of the spectrum, and children with classic GHD at the other, and a group of children with borderline to subnormal growth and partial GHD in between. At the same time there was a loosening of the "pass-fail" criteria for GH stimulation testing and a cutoff of 10 ng/mL rather than 5 to 7 ng/mL was adopted.<sup>23</sup>

Despite wide acceptance of neurosecretory GH dysfunction as a distinct clinical entity, there is much about this syndrome that is extremely ambiguous. There are, for example, no objective criteria for its diagnosis. Twenty-four-hour GH monitoring is expensive and labor-intensive, and has remained primarily a research tool. It also seems to be no better at diagnosing GHD than stimulated GH levels.<sup>24</sup> The diagnostic cutoff levels used during GH stimulation testing are recognized as arbitrary.<sup>25</sup> The finding of substantial discrepancies between one GH assay and the next, to the point that the diagnosis of GHD may depend on which assay is used, has highlighted the inadequacies of provocative testing.<sup>26</sup>

By default, therefore, a subnormal growth velocity often becomes the decisive factor in the decision to initiate GH treatment. However, the measurement of short-term growth velocity is itself subject to biases and inaccuracies. Growth velocities in the autumn and winter may be more than 2 cm/y lower than during the rest of the year, and a growth velocity of less than 2.5 cm/y during these seasons may be normal.<sup>27</sup> One study found that growth velocity was significantly higher after GH testing than before testing (3.4 cm/y versus 5.1 cm/y for prepubertal children and 3.4 cm/y versus 6.3 cm/y for pubertal children). An explanation for this odd finding may be that growth velocities prior to testing were transiently low, leading to a selection bias in referral.<sup>28</sup> The 95% confidence limits of a single height measurement performed by skilled personnel is  $\pm 0.5$  cm.<sup>29</sup> There is a similar lack of precision for measuring yearly growth velocities. For a short normal child growing along the 25th percentile, the confidence limits for yearly growth velocity span the 8th to 52nd percentiles. In general, the lower limit would be considered abnormal while the upper limit would be within the normal range. For measurements taken by inexperienced personnel or at less than 12 months apart, confidence limits would be even greater. Over 2 years, there is no correlation between year to year growth velocities, suggesting that short-term growth velocity is an unreliable means of predicting future growth.<sup>29</sup> The ambiguities surrounding the diagnosis of neurosecretory dysfunction no doubt account for some of the discrepancies in GH prescribing practices between one pediatric endocrinologist and another.

Recent interest in treating GHD adults has focused attention on the question, "What percentage of patients diagnosed with GHD in childhood truly have this condition?" The answer should give pause for thought. Tauber et al<sup>30</sup> found that 71% of 98 adults previously diagnosed as having partial GHD (peak GH response between 5 to 10 ng/mL) and 36% of 33 adults diagnosed with complete GHD (peak GH response <5 ng/mL) had normal stimulated GH peaks of greater than 10 ng/mL on a single stimulation test.

Not only is the diagnosis of partial GHD ambiguous, but the results of GH treatment also are unclear. For any child receiving GH, puberty appears to be an important dividing line in terms of therapeutic response. Testosterone and estrogen increase the amplitude of GH pulses, and a pubertal increase in GH accounts in part for the growth spurt of puberty.<sup>31</sup> This is, however, a 2-way relationship, as GH also influences pubertal

#### **In Future Issues**

**Molecular Physiology of Leptin and Its Receptor**  
Yiyi Zhong, PhD, and Ron L. Leibel, MD

**Growth Hormone Replacement In Adult GHD Patients**  
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**Insulin, IGF-1 and IDDM: Recently Implicated Genetic Loci**

Cheryl L. Deal, PhD, and Constantin Polychronakos, MD

sex steroid secretion.<sup>32</sup> GH treatment of GHD and non-GHD children to final height results in accelerated pubertal progression and a pubertal decrease in height standard deviation scores (SDS) for bone.<sup>33-36</sup> The acceleration in pubertal progression is dose-dependent. In a large group of male children with isolated GHD, a doubling of GH dose from 15 IU or 5 mg/m<sup>2</sup>/wk to 30 IU or 10 mg/m<sup>2</sup>/wk increased the rate of pubertal maturation but had no effect on growth velocity.<sup>37</sup> An earlier onset of puberty also was noted in a controlled study of non-GHD children, and this study concluded that therapy may actually have led to a decrease in final height.<sup>34</sup>

The implication of these observations appears to be that for children who are not truly GHD, the closer to puberty that GH treatment is initiated the less likelihood of a gain in final height. If treatment is started early in childhood, there is a greater chance of exceeding genetic potential. However, to accomplish this, supraphysiologic doses of GH need to be administered throughout childhood, resulting in a greater potential for long-term complications.

### Recommendations

Based on this discussion, I propose the following recommendations, appreciating that many of these points are out of line with the current practices of many pediatric endocrinologists:

1. The recommended dosage of GH treatment of 0.3 mg/kg/wk is a high one for the initial treatment of children with severe (classic) GHD. Treatment should be started at a lower dose and further dose changes titrated against the observed growth effect.

2. Families of short children who pass provocative testing and in whom pharmacologic GH treatment is contemplated should be informed that negative short-term data provide no assurance as to the ultimate safety of pharmacologic GH therapy and that the benefits of treatment in terms of final height are unknown. Families of children with Turner syndrome who are about to be placed on the newly recommended GH dosage of up to 0.375 mg/kg/wk also should be informed that there is little information on the short-term safety of this dose and none on its long-term safety.

3. For poorly growing peripubertal children, GH testing should be accompanied by sex steroid priming so as to exclude the transient, physiologic GHD present in many youngsters with constitutional delay of puberty. Sex steroid priming has gone out of favor in recent years, but could be used far more extensively.

4. A multicenter *controlled* trial should be organized to follow to final height children specifically with neurosecretory GH dysfunction or partial GHD treated with currently recommended doses of GH. It can no longer be taken for granted that these children benefit from therapy. Noncontrolled studies using estimated heights or historical controls are incapable of demonstrating conclusively the benefits of treatment. In my opinion, a study of this nature should take priority over other contemplated growth studies investigating new indications for GH treatment with ever increasing doses.

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This article was revised and updated from an article previously published in *Medical Hypotheses* (1995;45:523-528) with permission of the editor.

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