

## Diagnosis of GH Deficiency and GH Treatment

The availability of recombinant growth hormone (GH) has directed much attention to the diagnosis and treatment of GH deficiency (GHD). Rose et al of the NIH recently published in the *New England Journal of Medicine* an extensive analysis comparing the use of pharmacologically stimulated GH levels with spontaneous GH secretion—as determined by the GH levels over 24 hours—to diagnose GHD.

Three pharmacologic stimuli were used in 54 children with severe short stature. In 23, all GH values were  $\leq 7$  ng/mL, and these children were classified as GH-deficient on this basis. These results were compared with the mean integrated GH concentrations (ICGH). All 31 children who responded to pharmacologic tests with values  $>7$  ng/mL had ICGH

values in the range found in 46 normal-statured prepubertal children. Therefore, the authors conclude that no additional patients with GHD were detected and that the timely and costly measurement of ICGH in short children is of little diagnostic value.

The correlation between the results of the pharmacologic tests and ICGH levels in the GHD patients was poor, as only 57% of the 23 patients had ICGH levels below the range found in the 46 controls. Therefore, the authors recommend that the use of pharmacologic stimuli is sufficient to diagnose GHD.

The authors explain that the inclusion of more appropriate control subjects accounts for the discrepancy between their studies of ICGH with those of others. They postulate that the 43% of children with GHD, who had ICGH levels in the lower 20% of normal range, were children who require a higher GH level than most to grow nor-

mally; some defect reduced the spontaneous secretion of GH until it was in the lower normal range, and the defect was revealed after pharmacologic testing. Rose et al readily point out that further studies are indicated to determine how to best diagnose GHD.

They also report that the ICGH levels in the 46 controls did not correlate significantly with age, sex, height, weight, insulin-like growth factor (IGF-I) level, or growth velocity for age, although the IGF-I levels in the 31 short children without GHD were between the values seen in controls and GHD children.

In an editorial in the same journal, Grumbach addressed the use of GH therapy in GHD and short stature. He states that the criteria of Rose et al for the selection of short children for treatment with GH was rigidly defined and straightforward.

In the past, treatment was restricted to children with growth

velocities below the 25th percentile for age and GH levels  $\leq 14$  ng/mL on at least two provocative tests. However, conventional tests to define GHD have important limitations, including a paucity of standards that are related to age and sex in normal children. Also, there is growing concern about the variation in GH concentrations when kits from various commercial suppliers are used to measure GH levels.

Grumbach agrees that the observations of Rose et al are important and have practical implications. He agrees that the 24-hour GH profile remains a useful research tool but probably should not be used as a routine diagnostic procedure or in the selection of children with idiopathic short stature (ISS) for trial therapy with GH. He emphasizes that not one of the tests of GH secretion is, in fact, a useful discriminant in the selection of short healthy children for a trial therapy with GH. After excluding frank GHD by provocative tests, one acceptable approach is to categorize children with ISS as either responsive or unresponsive to GH over a 6-month period of treatment. This raises a most important question: Will the treatment increase the predicted height or merely lead to the attainment of adult height at an earlier age?

Ethical and economic issues must also be considered. For example, how will abuse of GH be avoided? Grumbach emphasizes that long-term, well-controlled studies to resolve the issues must be done promptly. He draws attention to the usefulness of oxandrolone, low-dose estrogen, and low-dose testosterone, all of which can be used as alternate therapeutic agents in certain short children (eg, those with constitutional delay of growth and Turner syndrome). His astute conclusion is that in considering GH treatment in children with ISS, we should recognize that the problem lies not in the GH profiles, but in the role of "heightism" in our society and the

psychosocial disadvantage it confers.

Rose SR, Ross JL, Uriarte M, et al. *N Engl J Med* 1988;319:201.

**Editor's comment**—Whoever says that life and the practice of medicine are easy has not visited the offices of doctors who treat short children. Although all agree that GHD is present in the patient with no response above 5 ng/mL (as determined by the GH assay utilizing the reagents and standards of the National Hormone Pituitary Agency), there are other short children who have partial GHD who will not be diagnosed in 1988 by pharmacological stimuli that test for GH adequacy. As pointed out by Reiter et al (*J Clin Endocrinol Metab* 1988;66:68), the results of GH concentrations vary widely with different assays. In our laboratory, the same serum specimen will yield a value of 4.0 ng/mL by the Hybritech assay and 8-12 ng/mL by the Nichols' kit assay. Some clinics using the same assay consider abnormal only values  $\leq 7$  ng/mL in response to a pharmacologic test; other clinics classify only values  $\leq 14$  ng/mL as abnormal. In addition, some of the short children with "normal" test results by accepted pharmacologic testing criteria will have low IGF-I concentrations and/or markedly delayed bone ages and/or low or low-normal ICGH levels. These patients may have GH inadequacy,

but not necessarily GHD, if GHD is interpreted as decreased GH production. GH inadequacy can encompass the production of a biologically inactive but immunologically active hormone or a partial resistance in generating IGF-I, which might be overcome with increased exposure to GH. The latter is comparable in concept to vitamin D dependency, a condition in which pharmacologic amounts of vitamin D are required to produce normal amounts of  $1\alpha,25$  dihydroxycalciferol.

Are these very short patients with possible GHD or inadequacy, whose physicians cannot agree on a uniform level of GH for interpretation of normalcy or on the GH assay to be used, to be deprived of GH? Rose et al and Grumbach have written that "further elucidation of what comprises GHD (and inadequacy) will need to be clarified, and the long-term effect of GH on ultimate height in ISS will have to be determined." In my opinion, a humane approach permits the occasional prescribing of GH on a trial basis for children with extreme short stature with possible deficiency of GH or inadequacy. However, all of us must prescribe judiciously to prevent abuse of GH. Most importantly we must be sympathetic, considerate, and supportive of those who are affected by the "heightism" in our culture.

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## Body Composition of Peruvian Children With Short Stature and High Weight for Height

Chronic undernutrition frequently occurs among children from underdeveloped countries. When combined with infectious diseases, it can result in a low height-for-age ratio and/or nutritional dwarfing. Paradoxically, nutritional dwarfing may also be seen in children with excess weight for height.

One hundred and thirty-nine Peruvian children, ages 6 months to 5 years, with nutritional dwarfing

but excess weight for height, were studied using both total body water measurements and detailed anthropometric assessment. Results of this study were compared with the National Center for Health Statistics (NCHS) Reference Standards. The mean weight-for-length/height of children in the study sample was above the 50th percentile and appeared to increase with age. In contrast, the

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