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Diagnostic Controversy: The Diagnosis of Childhood Growth Hormone Deficiency Revisited

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It has been known since the late 1950s that GH isolated from the pituitaries of humans and anthropoid apes was capable of stimulating growth in children with deficient GH secretion (1–3). Recombinant DNA-derived human GH (hGH) has been available for a decade and today, tens of thousands of children world-wide are receiving commercial recombinant hGH (4). Despite this dramatic progress in therapy, our ability to make a definitive diagnosis of GH deficiency (GHD) is often limited and relies on testing procedures that are, generally, nonphysiological, arbitrary, invasive, risky, and subject to considerable interassay variability. Given the clinical importance of a diagnosis of GHD as well as the expense of replacement therapy, a critical reevaluation of methods for establishing this diagnosis is warranted.

The foundation for the diagnosis of GHD in childhood (except for the neonate) must be auxology. Physicians caring for children should regularly measure and record heights and weights. Height determinations need to be made with appropriate measuring devices, such as infant boxes with firm horizontal surfaces and sliding perpendicular footboards, and Harpenden or wall-mounted stadiometers. Heights can be graphed on either cross-sectional or longitudinal growth charts, both of which are readily available. An unfortunate limitation of such charts is that they typically display heights only between the 5th and 95th percentiles (or 3rd and 97th percentiles). The development of growth charts with a range of 3 to −5 SD would greatly facilitate the documentation and reporting of abnormal heights. Sequential data can be plotted on appropriate growth charts; height velocity can be calculated from serial height determinations and plotted on appropriate velocity charts. Even with careful determinations, a period of at least 6 months (ideally, a year or longer) is necessary for reliable calculation of height velocity.

In the absence of other evidence of pituitary dysfunction, it is, generally, unnecessary to test GH secretion in a child growing at a normal velocity. Even in children who may be below the fifth percentile in height, careful documentation of a normal height velocity speaks strongly against the diagnosis of GHD. On the other hand, evidence of significant growth deceleration mandates thorough evaluation for potential causes of growth retardation, even if the child is still in the normal growth curve. Such patients require that nonendocrine causes of growth failure be excluded and thyroid function be documented to be normal before consideration of the possibility of GHD.

GH secretion

hGH is a single chain polypeptide comprised of 191 amino acids with an approximate mol wt of 21,500. Heterogeneity of circulating forms of GH results from posttranscriptional events, such as a messenger ribonucleic acid splicing variant leading to a 20-kilodalton (kDa) form, and posttranslational events, such as deamidation, acylation, phosphorylation,

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proteolysis, and aggregation (5). Normally, 70–75% of pituitary-secreted GH is in the 22-kDa form, with 20-kDa GH representing the second largest contributor to the circulating GH pool. The various molecular forms of GH in the circulation are subject to differing clearance rates in the kidney, with monomeric GH generally having the most rapid clearance (6, 7). Differential clearance rates have obvious implications for the relative proportions of various GH forms in plasma.

Short stature resulting from bioinactive, but immunologically reactive, GH has been reported (8–10). None of these cases has convincingly demonstrated the presence of an abnormal GH molecule, nor have naturally occurring mutations of the GH gene resulting in GH protein with decreased biological activity been identified to date. Studies evaluating GH bioactivity of serum from such patients have generally shown circulating GH to have normal affinity for its receptor (11).

GH circulates in plasma complexed to a specific, high affinity, low capacity binding protein (GHBP) (12–14). In humans, circulating GHBP appears to arise primarily from proteolytic cleavage of the membrane-associated GHR (15). Marked reductions in serum levels of GHBP have been identified in patients with GH insensitivity secondary to mutations or gene deletions in the GH-binding domains of the GH receptor (16–18). Carlsson *et al.* (19) demonstrated that the mean serum GHBP concentration in patients with idiopathic GHD is significantly reduced (−0.6 SD of the normal mean), but overlaps the normal range. Fewer than 5% of subjects with GHD have serum GHBP levels below −2 SD (19) Many children with idiopathic short stature also had reduced serum levels of GHBP, making this assay of little utility in the diagnosis of GHD. It is of note that Jan *et al.* (20) concluded that serum GHBP provides only a minor disturbance to conventional GH immunoassays.

Pituitary secretion of GH is pulsatile, with the most consistent surges occurring during slow wave electroencephalographic rhythms in phases 3 and 4 of sleep (21). The pulsatility of GH secretion is largely the product of the interplay of two hypothalamic proteins, GHRH (22) and somatostatin (somatotropin release-inhibiting factor, SRIF) (23). Regulation of GH secretion is complex, however, and also involves a large number of neurotransmitters and additional peptides, such as bombesin/gastrin-releasing peptide, galanin, and, potentially, opiate peptides similar to the synthetic GH-releasing peptides (24). Additionally, insulin-like growth factor-I (IGF-I) is capable of feedback inhibition on GH secretion, presumably by binding to specific receptors in the pituitary and suppressing GH gene transcription and GH secretion (25, 26). Spontaneous GH secretion varies significantly with age (27) and gender, and serum estradiol levels, in particular, correlate with 24-h integrated GH concentrations (28, 29).

GH stimulation tests

Between the pulses of pituitary GH secretion, serum GH concentrations are normally very low, typically below the sensitivity of most conventional assays (<0.2 ng/mL). Measurement of random serum GH concentrations is, consequently, of little value in establishing a diagnosis of GHD. Since the original observation of low or undetectable serum GH levels in fasting normal children (30), the use of physiological or pharmacological stimuli as a means of assessing GH reserve has been the cornerstone for the diagnosis of GHD (31). Physiological stimuli include sleep (21, 32), fasting (30), and exercise (33, 34). Pharmacological stimuli include L-dopa (35), clonidine (36), glucagon (37), propranolol (35), arginine (38), and insulin (39–43), among others. No single provocative test has been judged to be sufficient for the diagnosis of GHD, and tests are generally divided into screening tests, characterized by ease of administration, low toxicity/risk, and low specificity, and definitive tests, often characterized by higher toxicity/risk, but supposedly superior specificity. In truth, little justification for such classification has been provided. Additionally, to improve specificity, provocative tests are often administered sequentially or in combination (35, 44–46). Such combinations may be time-saving or cost-effective, but there is no objective evidence supporting claims that specificity or sensitivity is enhanced by performing tests in combination, rather than individually.

The limitations of provocative GH testing, the present "gold standard" in the diagnosis of GHD, include: 1) they are nonphysiological; 2) they rely on arbitrary definitions of what constitutes a subnormal response to stimulation; 3) they are age dependent, and the role of sex steroid administration has not been adequately defined; 4) they rely on GH assays of variable accuracy; 5) they are expensive, uncomfortable, and carry some risk; 6) their reproducibility has not been adequately documented; and 7) they can identify the child with severe GHD, but are of limited value in discriminating between normal short children and children with partial GHD. To some extent, at least, all of the above criticisms are valid (47).

Nonphysiological nature of provocative GH tests. None of the pharmacological provocative tests satisfactorily mimic the normal secretory pattern of pituitary GH. Although many of the agents employed to stimulate GH secretion mimic naturally occurring regulatory peptides or neurotransmitters, it is clear that in terms of dosage, route of administration, and interaction with other regulatory factors, all pharmacological provocative tests are artificial. Furthermore, there is no satisfactory way to resolve situations in which conflicting data arise from the use of multiple provocative tests (41, 44, 48–50). Customarily, a child who passes any one of multiple provocative tests is judged to have normal GH secretion. Although this may be valid in excluding severe GHD, it is of limited value in the diagnosis of partial GHD.

Arbitrary definitions of subnormal response to provocative GH tests. The definition of what constitutes a normal rise in serum GH concentrations after either physiological or pharmacological stimulation is largely arbitrary. In early reports of GH stimulation tests, a peak GH level of 5 ng/mL or more was typically employed to define a normal response (39, 41, 43, 49). Although it was recognized from the beginning that normal children could have variable responses to pharmacological stimuli, such as hypoglycemia or amino acid infu-

sion, this serum GH response seemed to best identify patients with a phenotype consistent with GHD. As experience with GH testing increased (and as the supply of pituitary hGH grew), most centers expanded the pool of children diagnosed with GHD by using a cut-off level of 7 ng/mL. With the increased availability of biosynthetic hGH, the serum cut-off level was generally increased to 10 ng/mL. No firm data exist to support any of these arbitrary serum cut-off levels for GH. The lack of clarity in the definition of GHD is evident in the use of terminology such as lack of adequate endogenous GH secretion (51) and inadequate secretion of normal endogenous GH (52),

Age dependency and use of sex steroids. Mean plasma GH concentrations increase during mid- to late puberty, primarily reflecting an increase in pulse amplitude (53–55). Twenty-four-hour GH secretion is particularly low in early puberty, making the distinction between true GHD and constitutional delay of growth and maturation problematic (56, 57). GH responsiveness to provocative stimuli is increased after the administration of estrogens (58) or androgens (59). Multiple reports can be found of children who failed provocative GH testing, but demonstrated normal responses after the administration of sex steroids or after spontaneous puberty (60–63). The interpretation of such results is open to debate. Marin *et al.* (64) recently studied a group of 84 normal-statured children between the ages of 4–20 yr who were given standardized treadmill exercise tests and arginine-insulin tolerance tests before and after the administration of ethinyl estradiol for 2 days. A marked age dependency of GH responsiveness was observed, with the lower limit of normal for peak serum GH rising progressively from 1.9 ng/mL in prepubertal children to 9.3 ng/mL at pubertal stage 5. Administration of estrogen increased the lower limit of normal for peak serum GH, with the lower 95% confidence limit for the normal range rising to 7.2 ng/mL and elimination of the correlation with pubertal stage. Thus, without sex steroid administration, 61% of the normal prepubertal children failed to raise their peak serum GH level after three provocative tests above 7 ng/mL and would have met the conventional criteria for the diagnosis of GHD.

Reliance on assays of limited accuracy. Recent reports indicate considerable variability in the measurement of serum GH concentrations by established radioassays (65–67). Discrepancies appear to relate at least in part to the molecular heterogeneity of circulating GH, the use of monoclonal *vs.* polyclonal antibodies, variability in GH standards, and the different diluents and matrexes employed in the assays. The net result is discrepancies among assays as great as 2- to 4-fold. Although all assays are characterized by some element of inaccuracy or imprecision, this degree of variability, when combined with the arbitrary and nonphysiological nature of provocative GH testing, markedly reduces the reliability of this diagnostic procedure.

Expense, discomfort, and risks of provocative GH tests. Many provocative tests require that multiple sequential samples be drawn; arginine-insulin stimulation, the most common standard, typically involves GH measurements on 10–12 samples. Additionally, some endocrine centers employ an outpatient screening GH stimulation test before arginine-insulin stimulation, which is typically performed in a day-hospital setting or during a clinic visit. The expense involved for such procedures and assays is considerable.

Provocative tests also involve some element of risk to patients. Virtually all pharmacological agents used to stimulate GH secretion have side-effects, including nausea, somnolence, and hypotension. Insulin-induced hypoglycemia may result in seizures, and the child with severe GHD may be particularly vulnerable. Deaths following the use of insulin-induced hypoglycemia as a GH test have been reported, from either hypoglycemia or overly vigorous replacement of glucose (68).

Poor reproducibility of provocative GH tests. Although there are many reports on the diagnostic use of the various GH secretagogues, there is a paucity of data on the reproducibility of such tests. Eddy *et al.* (69) evaluated repeat provocative test results in normal adult volunteers to determine the reproducibility of responses, defined as serum hGH increments greater than 5 ng/mL (a rather easily achieved response, because by current standards, a response would more generally be defined as a serum concentration >10 ng/mL). Reproducibility was achieved in nine of nine L-dopa tests, eight of nine insulin tests, six of nine arginine tests, four of nine vasopressin tests, and only three of nine glucagon tests. Zadik *et al.* (70) performed similar studies in a group of poorly growing children and observed a modest ($r = 0.487$) correlation in the results of clonidine stimulation tests ($P < 0.001$). No significant correlation was found in the results of repeat insulin or arginine stimulation tests ($P > 0.05$).

Limited ability to identify children with partial GHD. The studies cited above indicate that not only is there considerable variability from one stimulation test to another, but the reproducibility of response to any single stimulation test in patients other than those with complete GHD is marginal. As the definition of GHD has expanded, with progressive increases in the cut-off level of stimulated serum GH concentrations, the ability of stimulation tests to reproducibly discriminate between partial GHD and the child with constitutional delay or normal slow growth has been strained. Indeed, an argument has been made that constitutional delay itself represents a partial or transient GHD, even when such children, if left untreated, eventually accelerate their growth velocities and attain normal adult heights (71). On the other hand, it is also possible that the use of potent secretagogues in provocative tests masks the child with partial GHD or inadequate GH reserve. The term partial GHD continues to be problematic, because we are unable to provide an adequate definition of this category.

Measurement of spontaneous GH secretion

Several investigators have reported a poor correlation between spontaneous GH secretion and serum GH concentrations after provocative tests (72–75). Spiliotis *et al.* (76) argued that a subgroup of children with GH neurosecretory dysfunction exists. These children are characterized by normal provocative serum GH concentrations, but reduced mean 24-h serum GH concentrations, reduced number of GH

pulses per 24 h, and decreased mean peak GH pulse amplitude.

Many of the criticisms and limitations of provocative GH testing also characterize measures of spontaneous GH secretion. Such tests typically require blood sampling every 20 min for a minimum of 12 or 24 h. Assays of multiple serum samples (36–72 separate samples in 12–24 h, respectively) for GH concentrations is expensive and typically requires hospitalization. Alternatively, continuous serum sampling through a constant blood withdrawal system can be employed (77, 78), but such testing requires an in-dwelling catheter and does not permit analysis of GH pulsatility.

The reproducibility of measurements of spontaneous GH secretion has been reported to be superior to that of provocative tests (70, 79, 80), but variability remains a problem, and acclimatization to a hospital setting may be necessary in children (81). More importantly, considerable overlap may exist between values obtained in normal short children and children with GHD. Rose *et al.* (82) found that measures of spontaneous GH secretion identified only 57% of children with GHD identified by stimulation tests. Children with idiopathic short stature had normal mean 24-h levels of GH, with no evidence of neurosecretory dysfunction. Similarly, Lanes (83) found that one quarter of normally growing children had low overnight GH levels.

An alternative approach to the assessment of spontaneous GH secretion is the measurement of GH concentrations in urine (84). GH, however, is present in urine in very low concentrations (85–87), and assays require high affinity antibodies (88). At least 15 separate methods for immunoassay of urinary GH have been developed over the last decade (84), but the ability of such measurements to reflect pharmacological GH testing or to fully discriminate between abnormal and normal GH secretion remains unproven (89–91). Adequate age- and sex-related standards have yet to be developed, and it remains unclear whether GH excretion should be expressed relative to body weight or creatinine excretion, each of which may be problematic in the child with GHD.

Measurement of IGFs

The IGFs constitute a family of GH-dependent insulin-like peptides that mediate the growth-promoting actions of GH (92). Serum levels of the major GH-dependent peptide, IGF-I, are stable during the day, in large part due to the complexing of IGF peptides with a family of IGF-binding proteins (IGFBPs) (93). With the development of RIAs for IGF-I and IGF-II (94, 95), it became apparent that serum levels of these peptides reflected the GH status of the subject (96, 97).

IGF-I RIAs, however, have a number of significant limitations. Because the IGFs circulate in plasma complexed to high affinity IGFBPs, rigorous measurement requires separation of IGF peptide from BP (93, 98). IGF-I concentrations are also markedly age dependent (99), and in young children, the group in which one would most wish to facilitate the diagnosis of GHD, the normal range of serum IGF-I concentrations drops so low that it overlaps the range for GHD. Serum IGF-I concentrations may also be reduced in children with malnutrition (100), hypothyroidism (101), renal failure (98, 101), or diabetes (102). In addition to age dependency, serum IGF-I concentrations rise dramatically during puberty (99, 103, 104).

Multiple studies have shown that serum IGF-I concentrations do not correlate perfectly with GH status, as determined by provocative GH testing. In the study by Moore *et al.* (105), serum IGF-I concentrations permitted complete discrimination between GHD and normal short children only in subjects with bone ages greater than 12 yr. Reiter and Lovinger (97) found that 4 of 16 children with low provocative GH levels had normal IGF-I concentrations, whereas 7 of 25 short children with normal provocative GH levels had low IGF-I concentrations. Similarly, Cacciari *et al.* (106) reported that short normal subjects have IGF-I concentrations significantly lower than those of normal stature children. Neither baseline serum IGF-I concentrations nor GH-stimulated IGF-I levels are predictive of the growth response to GH therapy (107).

When serum concentrations of both IGF-I and -II are measured, there is an improved correlation with GH status, reflecting the fact that IGF-II concentrations are not as age dependent as IGF-I levels, but are still reduced in GHD (108). Although 18% of patients with abnormally low provocative GH levels had IGF-I concentrations within the normal range, only 4% of GHD patients had normal plasma levels of both IGF-I and IGF-II. Both IGF-I and IGF-II were reduced in only 0.5% of normal children and only 11% of normal short children. Nevertheless, even here, the correlation between serum IGF concentrations and measures of either provocative or spontaneous GH levels remains imperfect.

*Measurement of IGF*BPs

Of the six IGFBPs, IGFBP-3 is, normally, the major serum carrier protein for IGF peptides (93, 109, 110). Although each of the IGFBPs appears to be modulated by its own set of metabolic and hormonal regulators, IGFBP-3 is the most GH dependent (111). The development of specific RIAs for IGFBP-3 (111–114) has several potential advantages over assays for IGF peptides: 1) RIAs for IGFBP-3 are technically simple to perform and do not require separation of IGF peptides from BPs; 2) IGFBP-3 normally circulates in plasma at high levels, with normal concentrations in the microgram per mL range; assay sensitivity is not a problem; 3) although plasma concentrations are age dependent, the normal range varies only modestly with age; identification of abnormal concentrations in infancy or puberty is not, therefore, a problem; 4) plasma concentrations of IGFBP-3 are less nutritionally dependent than is the case with IGF-I; and 5) as IGFBP-3 is the major carrier protein for both IGF-I and IGF-II, its plasma concentration reflects both peptides.

Blum *et al.* (112) evaluated the utility of IGFBP-3 RIAs in the diagnosis of GHD. In children diagnosed as GHD by conventional criteria (height <3rd percentile, height velocity <10th percentile, and peak serum GH <10 ng/mL after 2 provocative tests), 128 of 132 (97%) had IGFBP-3 concentrations below the fifth percentile for normal age-matched controls. On the other hand, 124 of 130 (95%) of non-GHD short children had normal IGFBP-3 concentrations. Hasegawa *et al.*

(115) investigated the utility of IGFBP-3 measurement in children with complete GHD (peak provocative GH, <5 ng/mL), partial GHD (peak GH, 5–10 ng/mL), and normal short stature (peak GH, >10 ng/mL). In the group with complete GHD, the sensitivity of the IGFBP-3 RIA was 93% (100% in children >10 yr of age and 88% in children <10 yr old). In partial GHD, IGFBP-3 concentrations were reduced in only 43% of the subjects, whereas in normal short children, IGFBP-3 concentrations were normal in 88%. The reproducibility of IGF-I and IGFBP-3 assays was noted to be superior to that of GH stimulation tests (116).

Similarly, Smith *et al.* (117) found that 100% of children with severe GHD (peak GH, ≤1 ng/mL) and low IGF-I concentrations also had reduced IGFBP-3 concentrations. Four of 8 children with GHD and normal serum IGF-I levels had subnormal IGFBP-3 concentrations. Thirteen of 23 (57%) normal short children had normal IGFBP-3 concentrations. The addition of a RIA for IGFBP-2 enhanced the utility of IGFBP-3 and IGF-I measurements, as 50 of 57 (88%) of GHD children had IGFBP-2/IGF-I ratios greater than 2 SD above the mean.

As encouraging as these studies are, measurement of individual components of the IGF axis do not correlate perfectly with standard provocative GH testing. Even in healthy children, in whom a significant correlation exists between the spontaneous 24-h GH secretion rate and IGF axis parameters, such as serum IGF-I and IGFBP-3 concentrations, the correlation is modest ($r = 0.78$ for IGF-I and $r = 0.62$ for IGFBP-3) (118). In the study of Smith *et al.* (117), serum IGFBP-3 concentrations were discordant from the provocative GH response in 18% of the patients, and the IGFBP-2/IGF-I ratio was discordant with the GH response in 21% of the patients. It is important to recognize, however, that such discrepancies more likely reflect inadequacies of provocative GH testing (as detailed above) than limitations of measurement of IGF axis parameters. That this is likely to be the case is demonstrated by studies in patients with GH insensitivity (GHI) (119–121). Although such individuals have normal or even elevated GH concentrations, mutations or deletions of the gene for the GH receptor render them insensitive to GH action. These patients may, therefore, be considered to be functionally GH deficient. In a genetically homogeneous group of 70 patients in Ecuador (119, 121, 122), all were found to have profoundly reduced serum IGFBP-3 concentrations. Interestingly, despite the universally low IGFBP-3 concentrations and the characteristic severe growth failure, serum IGFBP-3 concentrations still correlated significantly with the height SD score (119, 121). In a heterogeneous group of GHI patients from around the world, Savage *et al.* (120) also found serum IGFBP-3 concentrations to be reduced in 100% of subjects. Indeed, Blum *et al.* (123) proposed that measurement of serum IGF-I and IGFBP-3 concentrations (both basally and in response to GH) be employed as a diagnostic criterion for GHI. Patients with a diagnosis of GHI, particularly when confirmed by molecular genetic studies, represent an excellent model of functional GHD, and it is clear that in such individuals, IGF axis parameters are unequivocally abnormal.

Summary and recommendations

Perhaps more important than the question of how to test for GHD, is the issue of whom should be tested. This decision should be based firmly on auxological criteria, with careful and accurate documentation of height velocity. In the absence of other evidence suggesting hypothalamic-pituitary dysfunction (*e.g.* hypoglycemia, microphallus, cryptorchidism, intracranial tumors, *etc.*), a child who is growing normally typically does not require evaluation of GH secretion. On the other hand, the child with evidence of central nervous system disease, such as an intracranial tumor or a history of cranial irradiation, should be tested for GHD when growth deceleration has been documented, even if the child's height is in the normal range.

If an alternative etiology for growth retardation has been identified (*e.g.* Turner's syndrome), testing for GHD is usually unnecessary. Appropriate disease-specific growth charts are being developed to enable the physician to ascertain whether a child with a known syndrome is growing at a rate consistent with that diagnosis. On the other hand, growth deceleration that is atypical for a specific syndrome must be considered to be compatible with coexisting GHD and merits further evaluation.

In view of the observations summarized above, it becomes clear that appropriate measures of the IGF axis provide an effective way to assess the GH status of a patient with short stature. For the patient with unequivocal GHD, IGF-I and IGFBP-3 are invariably reduced. For patients with milder abnormalities of GH secretion, serum concentrations of IGF-I and IGFBP-3 provide a meaningful measure of functional GH secretion and perhaps reflect GH status more effectively than does provocative GH testing. The fact that measures of the IGF axis do not invariably correlate with measures of spontaneous or provocative GH secretion speaks more directly to the inadequacies of our direct assessment of GH secretion than to limitations of IGF assays.

What, then, is the role of GH measurement? 1) Assessment of spontaneous or provocative GH secretion successfully identifies the patient with severe GHD, although this diagnosis can be readily established by reduced serum IGF-I and/or IGFBP-3 concentrations. Nevertheless, it is often of value to document impaired GH secretion, thereby verifying that decreased serum IGF and IGFBP-3 concentrations reflect an impairment of hypothalamic-pituitary function. Such studies would eliminate GH insensitivity as a cause of the patient's growth retardation. 2) Identification of a child with severely impaired GH secretion might suggest various hereditary forms of GHD, but such assessment inevitably requires more sophisticated molecular genetic studies. 3) When properly performed, data from GH testing, either provocative or spontaneous, can be integrated into the overall clinical profile of the patient. Confirmation of a severe defect of GH secretion should lead to appropriate imaging studies of the hypothalamus/pituitary, but such tests should also be obtained in patients with low IGF-I and IGFBP-3 concentrations and no other disease to explain these low values. Insulin-induced hypoglycemia as a test of GH secretion allows simultaneous assessment of the ACTH-adrenal axis, but

alternative tests can be readily employed for evaluation of ACTH secretion.

Ultimately, one is left to conclude that available methods for measuring GH secretion are neither convenient nor reliable. At the same time, it is important to recognize that serum IGF-I and IGFBP-3 concentrations can be influenced by factors other than GH secretion, such as malnutrition and liver disease. We conclude that the single most useful parameter in the assessment of the child with growth retardation is clinical evaluation, with emphasis placed upon accurate serial measurements of height and determination of height velocity. Additionally, a high index of suspicion is necessary in children with obvious predisposition to pituitary dysfunction, such as children with other pituitary disorders, brain tumors, septo-optic dysplasia, cranial irradiation, neonatal hypoglycemia, and/or microphallus, and hereditary forms of GHD. The diagnosis of TSH, ACTH, LH, FSH, or antidiuretic hormone deficiencies should support the diagnosis of GHD in the proper clinical setting. In the child with severe proportional short stature and documented subnormal height velocity, assessment of serum IGFBP-3 and IGF-I is warranted. Unless there is a family history of GHI or an elevated random serum GH measurement to suggest a diagnosis of GHI or the presence of clinically evident malnutrition or liver disease, subnormal serum levels of IGFBP-3 and IGF-I can be considered diagnostic of GHD. Although tests of GH secretion, whether spontaneous or provocative, remain of value, they should not be obligatory in the diagnosis of GHD. It must be recognized that there are patients with short stature, retarded height velocity, and low serum IGF-I and IGFBP-3 concentrations who can be considered to have disordered GH secretion even in the presence of normal provocative GH tests. Conversely, there are children who may fail provocative GH testing, whose growth patterns and serum IGF/IGFBP-3 concentrations argue against a diagnosis of GHD. Indeed, it may be reasonable to consider the diagnostic category of IGF deficiency, in which the various etiologies might include hypothalamic dysfunction, pituitary disorders, GH insensitivity, malnutrition, liver disease, *etc.*

The recommendations of this consensus statement should not be misconstrued to imply a proposed expansion of the current diagnosis of GHD or an increased market for commercial GH. Indeed, many children who might fail provocative GH testing and be erroneously diagnosed as GH deficient will be found to have normal IGFBP and IGF levels. Rather, we question the validity of GH measurements as the arbitrary gold standard for the diagnosis of GHD and suggest that careful auxological evaluation, supplemented by assessment of appropriate elements of the GH-IGF axis, provides the best foundation for a rational diagnosis of GHD.

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Erratum

The authors wish to correct a misprint that appeared in the article "Body Composition and Gonadal Steroids in Older White and Black Women," by Michael Kleerekoper, Dorothy A. Nelson, Edward L. Peterson, Paulette S. Wilson, Gordon Jacobsen, and Christopher Longcope (*Journal of Clinical Endocrinology and Metabolism* 79: 775–779, 1994). The values for androstenedione concentrations (mean ± standard deviation) in white and black populations should have been 4.18 ± 1.80 and 4.18 ± 1.46 nmol/L, and not 41.8 ± 18.0 and 14.6 ± 14.6 nmol/L as printed.