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Optimizing GH Therapy in Adults and Children

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Until the advent of modern neuroradiological imaging techniques in 1989, a diagnosis of GH deficiency in adults carried little significance other than as a marker of hypothalamopituitary disease. The relatively recent recognition of a characteristic clinical syndrome associated with failure of spontaneous GH secretion and the potential reversal of many of its features with recombinant human GH has prompted a closer examination of the physiological role of GH after linear growth is complete. The safe clinical practice of GH replacement demands a method of judging overall GH status, but there is no biological marker in adults that is the equivalent of linear growth in a child by which to judge the efficacy of GH replacement. Assessment of optimal GH replacement is made difficult by the apparent diverse actions of GH in health, concern about the avoidance of iatrogenic acromegaly, and the growing realization that an individual's risk of developing certain cancers may, at least in part, be influenced by cumulative exposure to the chief mediator of GH action, IGF-I. As in all areas of clinical practice, strategies and protocols vary between centers, but most physicians experienced in the management of pituitary disease agree that GH is most appropriately begun at low doses, building up slowly to the final maintenance dose. This, in turn, is best determined by a combination of clinical response and measurement of serum IGF-I, avoiding supraphysiological levels of this GH-dependent peptide. Numerous studies have helped define the optimum management of GH replacement during childhood. The recent requirement to measure and monitor GH status in adult life has called into question the appropriateness of simplistic weight- and surface area-based dosing regimens for the management of GH deficiency in childhood, with reliance on linear growth as the sole marker of GH action. It is clear that the monitoring of parameters other than linear growth to help refine GH therapy should now be incorporated into childhood GH treatment protocols. Further research will be required to define the optimal management of the transition from pediatric to adult GH replacement; this transition will only be possible once the benefits of GH in mature adults are defined and accepted by pediatric and adult endocrinologists alike. (*Endocrine Reviews* 22: 425–450, 2001)

Abbreviations: AGHDA, adult GH deficiency assessment; ALS, acid-labile subunit; AO, adult onset; BMD, bone mineral density; BSAP, bone-specific isoenzyme of alkaline phosphatase; CO, childhood onset; FM, fat mass; GC, glucocorticoid; GGSG, Genentech Growth Study Group; GHBP, GH binding protein; GHD, GH deficiency; IGFBP, IGF binding protein; KIGS, Kabi International Growth Study; LBM, lean body mass; NCGS, National Co-operative Growth Study; NHP, Nottingham Health Profile; PGWB, Psychological General Well-Being Schedule; QoL, quality of life; rhGH, recombinant human GH; SST, somatostatin; TBK, total body potassium; TBW, total body water.

I. Introduction

IT IS NOW more than a decade since the publication of the earliest double-blind placebo-controlled studies of the use of recombinant human GH (rhGH) in patients with adult-onset (AO) GH deficiency (GHD) (1–5). In the intervening years, increasing attention has been devoted to devising treatment protocols that maximize the potential clinical benefit of treatment with GH, while trying to minimize the risks that may result from prolonged excessive GH exposure. In the original trials of GH replacement therapy for

adult hypopituitarism, GH dose was calculated on the basis of weight and/or surface area (1–5). This was essentially done as an extension of pediatric practice, as there was little or no experience of GH therapy outside the pediatric setting at that time. With time and shared clinical experience, it has become apparent that such a dosing strategy was too simplistic and that the dose of GH needs to be individually tailored for each patient (6, 7). In retrospect, this was predictable, given that all other endocrine replacement therapy needs to be carefully adjusted for each patient, reflecting the wide variation in secretion and/or clearance rates, of glucocorticoids, thyroid hormone, and gonadal steroids in healthy subjects. Paradoxically, it is the increasing use of GH for the treatment of AO hypopituitarism that has led to a more thorough examination of the physiological role of GH after the completion of linear growth. Inevitably, the recent experience in adult clinical practice has prompted a critical reevaluation of the strategies used for the management of GHD in childhood. This article will review the current clinical practice of GH therapy for the attainment of final height in children. It will then discuss methods of GH dosing in adults with specific reference to our current state of knowledge about the normal physiology of GH secretion and action after the completion of linear growth. The issues that surround reassessment of GH status in GHD children once final height has been achieved and the decision as to whether to continue with GH therapy in this patient group will also be reviewed. The article will conclude by examining, in the light of recent clinical experience in GH dosing for adults, whether the time has come for a closer examination of GH dosing strategies used in pediatric clinical practice.

II. Physiology of GH Secretion and Action

In any discussion about optimizing GH dosing schedules, it is important to remember that reproduction of normal physiological patterns of GH secretion and action is limited by available modes and routes of administration of exogenous GH. Hence, as with other forms of endocrine replacement therapy (such as glucocorticoid replacement for patients with primary or secondary adrenal failure), the aims of the treating physician are limited to a maximization of clinical benefit while minimizing the risks of excessive exposure.

GH is released from anterior pituitary somatotrope cells in a pulsatile fashion, with surges of GH release punctuating long periods when GH levels in plasma are very low and detectable only by sensitive chemiluminescence assays (8) (Fig. 1B). GH release, in turn, is stimulated by GHRH and inhibited by somatostatin (SST), both of which are produced by the hypothalamus (for review see Ref. 9). A separate receptor exists, the GH secretagogue receptor (10), the ligand for which (*Ghrelin*) has recently been cloned (11). The details of the neuroendocrine mechanisms by which these various inputs interact to regulate GH release, and in particular the precise role of Ghrelin, are not fully elucidated, but the simplest model postulates that a simultaneous drop in SST tone, together with bursts of GHRH secretion, is responsible for the generation of a GH pulse (12).

GH is a 191-single polypeptide chain that exists in the circulation partially bound to two separate GH binding proteins (GHBPs), one of high (13) and one of lower affinity (14). The higher affinity GHBP is the extracellular portion of the GH receptor, two of which bind to different regions of the GH molecule, with subsequent dimerization triggering GH-mediated cellular activation (15). Although it is believed that levels of GHBP in the circulation may be an indicator of the number and/or activity of GH receptors, a major negative determinant of GH-BP levels in health is abdominal obesity (16). This has obvious implications for GH dose selection and monitoring, because the bioactivity of the same dose of GH given to two people of equivalent age, sex, and gonadal status will depend, at least in part, on their respective degrees of visceral obesity.

The GH secretory pattern, hepatic GH receptors, and circulating GHBP levels are closely interrelated. In the rat, linear growth is most sensitive to pulsatile GH exposure and peak amplitude, whereas GHBP and hepatic GH receptor levels are regulated separately by the level of continuous GH baseline exposure (17). As in rats, baseline GH levels are higher in females than males (18–21), although the magnitude is less apparent. Short-term comparisons of continuous *vs.* pulsatile GH treatment in man have so far revealed only minor differences in metabolic parameters (22, 23), but longer treatment in GH-deficient children shows induction of GHBP after continuous, but not pulsatile, GH treatment (24). It has been suggested that the GH pattern is important for growth in man, since increasing the frequency of GH

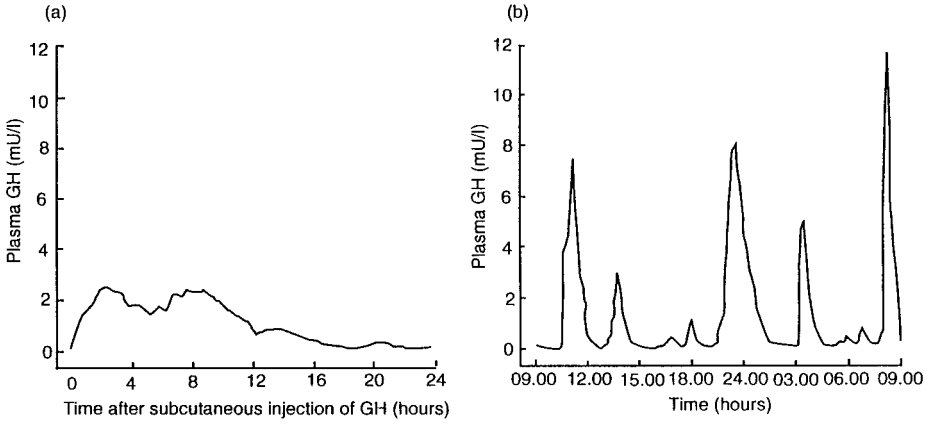

FIG. 1. Plasma time-curve for GH 1.2 IU given by injection to an adult with GHD (a) compared with the physiological pattern of GH secretion in a healthy middle-aged male (b). [Courtesy of Dr. Y. Janssen, personal communication].

therapy to daily injections improves its growth-promoting effect (25–27), although in the short term once daily subcutaneous injections stimulated growth equally well as continuous subcutaneous infusion in GH-deficient children (24).

GH has some direct effects on peripheral tissues, most notably epiphyseal chondrocytes (28), but the majority of its actions are mediated through the peptide hormone insulin-like growth factor-I (IGF-I), a member of the insulin-like gene family. Almost all IGF-I in the circulation is bound to one of several IGF binding proteins (IGFBPs), the most abundant of which is IGFBP-3. Together with the acid-labile subunit (ALS), IGF-I and IGFBP-3 (levels of which are all GH dependent) form a ternary complex of 150 kDa. This prolongs the half-life of circulating IGF-I and ensures that levels in a given individual remain stable throughout the day. However, the simplistic use of serum IGF-I measurements as a precise marker of overall GH status is flawed because of the many variables that affect both hepatic and local tissue IGF-I production in response to a given GH stimulus. Most strikingly, GH-mediated IGF-I production varies with gender. Analysis of 24-h GH profiles in normal weight, middle-aged, healthy volunteers shows that to maintain an equivalent serum IGF-I level, mean daily production is approximately 3 times greater in women than in men, due largely to an amplitude-specific divergence in the pulsatile mode of GH secretion (29). Most circulating IGF-I is derived from the liver, but it is also generated in nonhepatic tissues where it appears to function in an autocrine/paracrine fashion (30). IGF-I generation in response to a given GH stimulus may be modulated by local tissue-specific factors, of which gonadal steroids are an important example. Testosterone administration to normal men and those with hypogonadotropic hypogonadism increases serum IGF-I levels, while oral estrogen therapy improves the signs and symptoms of acromegaly (31) and lowers serum IGF-I levels in normal postmenopausal women (32). Furthermore, estrogens have different effects on GH secretion and action depending on the route of administration. Oral ethinyl estradiol attenuates IGF-I production despite a 3-fold increase in mean 24-h GH, whereas transdermal 17β-estradiol does not alter overall GH secretion but causes a slight increase in circulating IGF-I (33, 34). Such changes are almost certainly physiologically important, on the basis of changes in markers of connective and bone tissue activity that parallel the changes in serum IGF-I levels (35).

As with other hormonal systems, GH, IGF-I, and the hypothalamic peptides SST and GHRH form a complex feedback system at various levels. For example, exogenous GH administration attenuates the size of subsequent GHRH-mediated GH secretion, apparently independently of circulating IGF-I levels (9, 36), and there is evidence that hypothalamic GH receptor expression is suppressed by GH (37). There are also data to suggest feedback regulation of GH secretion by IGF-I (38).

A. Changes in GH and IGF-I levels with age

GH secretion continues throughout life (39, 40) and this, together with the clinical features of adult GH deficiency and the observed favorable effects of GH on hypopituitary patients, forms a persuasive argument that GH may have important physiological functions after the completion of linear growth. Rates of GH secretion increase with the onset of sexual maturation, reaching approximately 2–3 times their prepubertal levels by mid-late puberty (39, 40). Thereafter, GH secretion rates decline by approximately 14%, and the half-life of GH shortens by 6% with each passing decade (39, 40). The reasons for this fall are not entirely clear, although a reduction in responsiveness to injected GHRH and an increase in SST have been documented *in vivo* in the rat (41, 42). In humans, repetitive administration of GHRH to elderly men partially reverses the age-related decline in responsiveness to this peptide (43), suggesting that failure of hypothalamic GHRH release may, at least in part, underlie the age-related fall in spontaneous GH secretion. Furthermore, concurrent with the suggestion that SST is increased in older individuals, coadministration of arginine enhances the GH-releasing activity of a GH-releasing hexapeptide in healthy elderly, but not young, subjects (44). These age-related changes in GH secretion are largely paralleled by a decline in serum IGF-I levels in both men and women (45). However, the positive relationship between serum IGF-I and spontaneous 24-h GH secretion becomes less striking with age (46). This may, in part, reflect increasing obesity with advancing years. An inverse correlation has been demonstrated between adiposity and plasma IGF-I levels (47, 48), although separation of this from the known effects of obesity on GH secretion (40) is difficult.

III. Pharmacokinetics of Administered GH

rhGH is almost universally administered subcutaneously (Fig. 1A). Most studies report the time to reach peak level (C_{max}) is around 4–6 h after an injection, with a length of disappearance of 20–24 h (49, 50); these figures correlate well with the kinetics of insulin absorption in patients with diabetes (51). Studies comparing the bioavailability of GH by continuous infusion and bolus injection show significantly lower GH levels with subcutaneous administration compared with intravenous, suggesting a degree of local subcutaneous degradation (52, 53). The volume of injection may also be important. Injection of 6 IU GH in three separate volumes on separate occasions to normal individuals showed that the use of a larger volume resulted in a higher C_{max} and a greater area under the curve, implying greater overall bioavailability (54).

It is apparent, therefore, that the GH/IGF-I system, like other endocrine systems, is a dynamic one, the activity of which changes with age, sexual maturation, body composition, and other factors. Clearly, it is not possible to recreate normal physiology with a single subcutaneous injection of GH, so the goal of treatment of GHD is correction of the associated clinical syndrome. In children, failure of linear growth is an almost universal presenting feature, whereas in adults the diagnosis of GHD almost invariably is made in patients with a background of known hypothalamo-pituitary disease.

IV. Review of Pediatric Practice

GH deficiency during childhood is associated with severe growth retardation resulting in marked impairment of adult height. GH therapy for GH-deficient children was first used in the 1950s with hormone extracted from the pituitary glands of cadavers (55). Because of the limited supply, suboptimal doses of pituitary GH were administered initially in a standard fixed dose, independent of size, two to three times weekly, and the response to therapy was modest. Burns *et al.* (56) reported on the final height of 55 GHD children treated before 1981. GH was administered at a dose of either 10 IU twice weekly or 5 IU three times a week, irrespective of weight or surface area. Treatment was begun between the ages of 9 and 14 yr in most of the children, and therefore a total weekly dose of 15–20 IU represented a suboptimal GH dose by modern standards. The smaller children, however, would have initially received a fairly high dose relative to their size. At completion of growth, average height was more than 2 SD below the population mean, with stature in more than half the children failing to exceed the third centile. The response to therapy did not differ between those treated with two or three injections per week, despite a significant difference in total dose received, suggesting that frequency of injections is important. Other early final height studies also reported a modest response to GH replacement, with adult heights not always significantly greater than those observed in untreated individuals (56–59). In 1985, the first reports emerged of the link between pituitary-derived GH therapy and Creutzfeldt-Jakob disease (60), and human GH was promptly withdrawn. However, within a year GH produced by recombinant DNA technology became available (61). In addition to negating the risk of Creutzfeldt-Jakob disease, synthetic GH also transformed the practice of GH replacement by providing a potentially limitless supply of therapy. This allowed the treatment of GHD children with higher, more appropriate doses, and also enabled GH therapy to be offered to a much wider range of patients. Subsequent studies have helped define which patients benefit from GH therapy and the optimal dosing schedules.

A. Diagnosis of GHD and patient selection

In pediatric practice, the diagnosis of GH deficiency is usually suspected on the grounds of auxological data, although a minority of children are diagnosed because of known pituitary disease or after radiotherapy involving the hypothalamo-pituitary region. Selection of the patients most likely to derive clinical benefit from GH therapy demands a sensitive and specific test that distinguishes GH-deficient from normal subjects. A number of approaches have been used to confirm GHD in childhood, including GH stimulation tests, 24-h GH profiles, urinary GH, and measurements of IGFs and IGFBPs (62–64). There is no single test, however, that can invariably distinguish normal children from GH-deficient individuals, particularly those with less severe degrees of GHD.

Provocative tests remain the standard method of confirming a diagnosis of GHD in a child in whom the diagnosis is suspected on the basis of auxological data, or a predisposing factor (64). A number of different agents have been used including insulin, arginine, glucagon, propranolol, clonidine, and L-dopa (63). Physiological stimuli, such as sleep, fasting, and exercise, have also been employed. The definition of what constitutes a normal rise in serum GH concentration after either physiological or pharmacological stimulation is largely arbitrary. In early reports, a stimulated peak GH level of 5 ng/ml or more was considered to be indicative of normal GH reserve. This definition has gradually changed, influenced to some extent by the increased availability of therapy after the advent of rhGH, such that a level of between 7 and 10 ng/ml is now generally accepted as the cutoff. IGF-I and IGFBP-3 levels have also been used as a measure of GH status, and it has been suggested that the use of a combination of tests improves diagnostic accuracy (62). However, there remains no method of reliably separating all GH-deficient children from GH-replete subjects, and this difficulty is reflected in the retest data, which suggest that a substantial proportion of children treated for GHD during childhood have entirely normal GH responses to standard tests in adult life (65). In practice, the diagnosis of GHD is based on careful clinical assessment, augmented by a number of tests, which reflect GH status (63).

B. GH treatment: dose and schedule

There is good evidence that GH therapy should begin as soon as possible to optimize long-term growth (66–68). Prompt initiation of therapy is particularly important in young children in whom fasting hypoglycemia may complicate GHD (69). While there is broad agreement about the optimal timing of the start of therapy, the selection of the appropriate GH treatment dose is less clear.

There are several methods that may be employed for defining the optimal replacement regimen in GH-deficient patients. Attempts can be made to mimic normal physiology by administering GH at doses that approximate to normal production rates, or by attempting to achieve serum levels of GH or GH-dependent markers that are close to normal levels. Alternatively, treatment may be selected on the basis of the reversal of the biological endpoints of GHD, while minimizing any adverse effects of therapy. In pediatric practice, the selection of optimal GH doses and treatment schedules has rested almost entirely on the response to therapy in terms of linear growth.

Some attempts have been made to define physiological GH requirements by examining GH production in normal subjects, or by measuring biochemical markers of GH status in treated patients. Studies in healthy children have estimated daily endogenous GH production to be approximately 20 μg/kg/d (equivalent to 0.14 mg/kg/week) (70, 71), rising to 35 μg/kg/d in late puberty (71), although considerable interindividual variability exists (72–75). Extrapolating this to replacement doses is hampered by the different pharmacodynamics of exogenous GH administered subcutaneously, but it does provide an estimate of GH requirements. Few data exist regarding the measurement of GH markers during replacement therapy in children. Hibi *et al.* (76) measured plasma IGF-I, urinary IGF-I, and urinary GH in a cohort of GH-deficient children and suggested that a GH

dose of 0.16 mg/kg/wk was close to a physiological replacement dose. A more recent study has documented serum IGF-I and IGFBP-3 levels within the normal range in a group of GHD children receiving a mean GH dose of 0.17 mg/kg/wk. Furthermore, in a large multicenter randomized US trial (n = 139), girls with Turner syndrome received either 0.27 mg/kg/wk or 0.36 mg/kg/wk of GH in combination with either low-dose estrogen or oral placebo, and only 1.4% had serum IGF-I levels greater than 2 SD above the mean for age (77). In contrast, in a smaller study of 31 patients, Tillman *et al.* (78) reported two of 20 GHD and three of seven children with Turner syndrome showed supraphysiological IGF-I levels during the first year of GH treatment. As the measurement of IGF-I during childhood GH therapy becomes commonplace, more information will become available regarding IGF-I levels achieved with different GH doses. It is clearly important that normative data should be accumulated across the childhood age range.

The vast majority of clinicians have used the growth response to GH therapy to define the optimal replacement dose. The endpoints used to define the benefits of different doses have been both short-term growth and growth velocity and, more importantly, final height. It was recognized before the advent of rhGH that a dose-response relationship exists between GH dose and growth rate (79, 80), and more recent data have confirmed that GH dose influences the short-term growth response to GH replacement (81, 82). In addition, dose frequency has been shown to be an important factor in determining the response to therapy. Changing from three times a week to a daily subcutaneous injection results in an increased growth rate for a given total GH dose (83, 84), although no further growth advantage has been demonstrated with more frequent injections (84–86). With the greater availability of rhGH, higher GH doses have generally been used, and this has resulted in more favorable final height data. Despite reasonable improvements in height SD scores (the number of SD scores by which an individual's height differs from the mean for his/her age and sex) during treatment with pituitary-derived GH, average final height in these children was only −2.3 SD scores (87). The vast majority of patients treated with rhGH, however, achieve a final height within the normal range, with an average final height of −1.4 SD score (87). In the last 5 yr a number of groups have published data from cohorts of children treated with rhGH to final height (66, 68, 87–92). Height gain in these studies, as assessed by the difference between final height and predicted adult height or initial height SD score, ranged between 0.8 SD and 2.4 SD, with average final height ranging between −2.1 SD and −0.7 SD. The criteria used to diagnose GHD and therapeutic regimens employed varied between the studies and probably account for much of the variation in the results.

These data confirm the benefits of treatment with a weekly dose of at least 0.15 mg/kg but controversy remains concerning the additional benefits of higher doses. Analysis of final height data suggests that a dose between 0.17 and 0.3 mg/kg/wk is a reasonable replacement dose (70). The most reliable data are taken from large multicenter studies such as the Kabi International Growth Study (KIGS), the National Co-operative Growth Study (NCGS), and the Genentech Growth Study group (GGSG). Interpretation of data from these large cohorts of patients is complicated by the fact that they were collected over a number of years from many different centers, and there is therefore a degree of variability in the treatment protocols employed. Thus, a proportion of patients have received treatment that is now considered suboptimal, and the responses to therapy need to be assessed with this in mind. In addition, some of the differences observed in the response to therapy may be due to differences in the study populations. Data from the GGSG (66) suggest that treatment with 0.3 mg/kg/wk is associated with significantly greater improvements in final height than those observed in patients enrolled into KIGS, who received a lower average dose of 0.16 mg/kg/wk (88). The GGSG cohort achieved a final height of −0.7 SD compared with −1.5 in the KIGS group. However, the midparental height of the GGSG cohort was significantly greater than that in the KIGS group, and, after correcting for this, there was no difference in final height achieved (88). In addition, data from the NCGS in a larger cohort of GH-deficient children treated with 0.3 mg/kg/wk demonstrated a more modest response (68) similar to that seen in the KIGS patients (final height −1.4 SD). However, analysis of a separate cohort of Swedish patients within KIGS treated with an intermediate dose of 0.22 mg/kg/wk demonstrated complete normalization of final height, indicating that higher doses may result in a better response to therapy (88). Furthermore, a recent report suggested a significant short-term growth advantage from a GH dose of 0.35 mg/kg/wk over that observed with 0.17 mg/kg/wk (93). A further increase in the dose to 0.7 mg/kg/wk conferred no additional benefit, and this concurs with other studies that have examined the use of higher GH doses (70, 94). In accordance with all these data, recent internationally agreed guidelines for the treatment of GH deficiency in childhood suggest a dose of 0.17–0.35 mg/kg/wk (95).

Ultimately, the selection of the replacement dose is based on interpretation of the available data, local availability of GH, and also on financial grounds. Given the variability in GH production in normal individuals, it is likely that GH requirements will vary from patient to patient, and a more individual approach may eventually be required. This would necessitate an accurate method for assessing and monitoring the appropriateness of a given GH dose in each patient.

C. Puberty

GH production in normal individuals rises during puberty (71). In addition, a positive correlation has been found between total pubertal height gain and mean GH dose during puberty (96). It has therefore been suggested that the dose of GH replacement should be increased at the onset of puberty to mimic normal physiology. Stanhope *et al.* (97), however, demonstrated no increase in growth rate on increasing GH dose from 15 IU/m^2/wk to 30 IU/m^2/wk during puberty in a small cohort of GH-deficient children, compared with a control group who continued on 15 IU/m^2/wk. Indeed, their data suggested that a high GH dose accelerated the progression through puberty and may therefore be detrimental to final height outcome. It should be noted, however, that their conclusions were based on the short-term growth response, and these children were not followed to final height. More

recently, Albertsson-Wikland *et al.* (98) demonstrated no increase in total pubertal height gain in boys treated with 0.42 mg/kg/wk compared with boys treated with 0.21 mg/kg/wk. In addition, MacGillivray *et al.* (70) compared data between several large studies of GH replacement employing differing doses of GH. Pubertal height gain did not differ significantly between the cohorts, suggesting no additional benefit from a higher replacement dose during puberty (70). Thus, while some centers still advocate an increase in GH dose at puberty, many clinicians continue treatment at a similar dose (calculated per kg or m^2) throughout childhood.

The most likely explanation for the lack of a significant growth advantage with an increased GH dose during puberty is that this is associated with an advance in bone maturation. This will lead to earlier fusion of the epiphyses and therefore shorten pubertal growth, and it has thus been suggested that pharmacological delay of pubertal development may improve the overall growth response to GH replacement. Delaying the progression through puberty by the administration of GnRH analogs has been standard practice for the treatment of precocious puberty for a number of years. The main long-term goal of this therapy is to prevent reductions in adult height, which will occur if puberty is allowed to progress at an early age, because of the reduced time available for linear growth. Improvements in final height have been achieved with GnRH analog therapy in precocious puberty (99–101), although some authors have suggested that the addition of GH therapy may further improve growth. A few studies have examined the effects of combined treatment with GH and GnRH analogs in children with precocious puberty and normal GH levels (102, 103). In addition, there are a number of reports of combined treatment in children with both GHD and early puberty (104, 105). The use of combined therapy has also been investigated in short normal children (103, 106–108). The results of these studies have been variable, with many showing little improvement in growth velocity or final height. Nonetheless, it has been postulated that GnRH analog therapy may augment the growth response to GH therapy in GHD. A few studies have suggested improvements in final height prognosis with a combination of GH and GnRH therapy (109–112). Some of these reports have been limited by the use of final height predictions based on the short-term response to therapy. The recent report from Mericq *et al.*, however, followed 21 GH-deficient subjects to near-final height defined as a bone age of 14 yr in girls and 16 yr in boys (111). Patients were randomly assigned to GH therapy plus LHRH analog of GH alone. A significant gain in near-final height was demonstrated for those receiving combination treatment compared with those treated with GH alone (mean height SD score −1.3 *vs.* −2.7), with no alteration in body proportions. This was achieved at the expense of significantly delaying puberty, with the mean age at menarche in the girls treated with LHRH being 18.2 yr compared with 15.9 yr in the GH-alone group. Thus, while these data are promising in terms of potential height gain, the psychosocial implications of pubertal delay need to be balanced against the growth advantage that is potentially conferred by the addition of GnRH analogs to GH therapy. In addition, the number of patients who have been followed to final height remains small, and further data are required before the addition of GnRH analog therapy can be routinely recommended for use in GH-deficient children in the absence of coexisting precocious puberty.

D. Side effects of GH therapy

There are a number of adverse effects that have been attributed to GH replacement during childhood. The most comprehensive data are available from large international surveillance studies that have been specifically designed to monitor safety of treatment. Idiopathic (benign) intracranial hypertension was first reported in 1992 (113), and a number of subsequent reports have confirmed the relationship with GH therapy (114–118). Data from the NCGS and KIGS databases have revealed 35 cases of idiopathic intracranial hypertension from a total of more than 40,000 patients receiving more than 109,000 yr of GH therapy (114, 117). The condition improves after withdrawal of therapy, and GH can often be restarted without a recurrence of the problem.

The question of the impact of GH therapy on tumor growth has often been raised, particularly with reference to populations of children previously treated for childhood malignancies. Because interpretation of tumor recurrence data is complicated by biases introduced by the selection of children for GH therapy, careful matching of control populations is necessary. The available data do not suggest any increase in the risk of tumor recurrence in the children after GH treatment; both single-center studies (119) and large-multicenter surveillance studies (114, 120) have failed to show any increase in the incidence of *de novo* malignancies during GH replacement. Fasting glucose levels have been shown to rise after the commencement of GH therapy in children (121), and there have been reports of the development of diabetes mellitus during treatment (122). Data from the NCGS (117) and KIGS have not suggested an increase in the incidence of type 1 diabetes, but the KIGS database did demonstrate a higher than expected incidence of type 2 diabetes in a heterogeneous population including children treated with GH for short stature not due to GHD (123). The incidence was, however, very small (34 cases per 100,000 yr of GH treatment), and it was postulated that the higher rates may indicate an acceleration of the disorder in predisposed individuals.

A number of other adverse events occur more commonly during GH therapy in children. Slipped capital femoral epiphysis (117, 124), gynecomastia (116), and juvenile osteochondritis (114) have all been reported during treatment, although a direct causal relationship with GH has not been established. Interestingly, edema and carpal tunnel syndrome only occur only very rarely in pediatric practice (117), although these are commonly reported in adult-onset GH-deficient patients receiving GH replacement (125). The reason for this discordance is not clear.

E. Predictors of response to therapy

Several reports from large cohorts of GH-deficient children have provided some information on factors that influence the growth response to GH replacement (51, 66, 72, 73, 76, 82, 88, 89, 92, 108, 126). Analysis of the KIGS database

suggested that first year height velocity was negatively correlated with age and height SD score and positively correlated with birth weight, weight at beginning of therapy, GH dose, frequency of injection, target height SD score, and degree of GHD, as judged by the peak GH response to a stimulation test (81, 127). Analysis of final height data demonstrated no effect of GH dose on adult height, although the duration of GH therapy was a significant factor (88). This underscores the need to begin GH therapy as early as possible to attain the maximum final height, and also suggests that, within the dose range used (10th–90th centiles; 0.11–0.24 mg/kg/wk), variations in weekly GH dose has little effect on final height. Data from the NCGS are consistent with these findings, suggesting that the initial response to GH therapy may be predicted by age, degree of GHD, weight adjusted for height, GH dose, injection frequency, and midparental height (82). Final height was dependent on pretreatment height and age, duration of treatment, sex, and first year growth rate (66). Thus, knowledge of a number of baseline parameters will help predict the response to therapy. From these data, models have been developed that allow reasonably accurate prediction of the first year growth velocity after GH therapy. However, although a greater initial response to treatment will be psychologically important to the patient and is likely also to improve compliance, the final height achieved is generally considered to be the most important goal of therapy. The model developed from the KIGS database (127) has been extended to examine second, third, and fourth year growth response and has demonstrated that first year height velocity is the most important predictor of subsequent growth. Extrapolation of these results would suggest that first year height velocity is likely to be an important determinant of final height; however, this has yet to be established, and at present these models can predict only the initial growth after the institution of GH replacement and not the overall response to therapy.

There are also a number of other markers that may help predict the initial growth response. Markers of bone turnover are significantly reduced in GH-deficient children and increase after GH replacement (128). The increase in serum bone alkaline phosphatase levels (a marker of bone formation) after 3 months of GH replacement has been shown to correlate with improvements in the height SD score in the first year of therapy. Serum leptin levels also alter with GH status, predominately as a result of changes in fat mass and distribution. Leptin levels reduce during GH replacement (129), and changes in leptin concentration 1 and 3 months after the beginning of GH therapy have been shown to correlate with growth in the first year of treatment (130). These observations of changes in bone alkaline phosphatase and serum leptin indicate that metabolic markers are potential predictors of the short-term growth response to GH therapy.

Standard GH replacement therapy in GH-deficient children thus consists of daily injections of rhGH, usually administered at a weight-based dose of between 0.17 and 0.3 mg/kg/wk. Treatment is initiated as soon as possible once the diagnosis has been made and is continued until the attainment of final height. This is usually defined as either a slowing of growth to an annualized height velocity of less than 1 cm/yr or the demonstration of fusion of the long bone epiphyses (131). Improvements in linear growth have been almost the sole indication for the use of GH in pediatric practice. There are some data, however, concerning the use of GH in normally growing GH-deficient patients after surgery for craniopharyngioma (132), which demonstrated beneficial metabolic effects of treatment resulting in advantageous changes in body composition and suggested that GH replacement is indicated in these children despite their normal growth. In addition, data from the use of GH therapy in children with Prader-Willi syndrome have demonstrated beneficial effects of treatment on body composition, muscle strength, and respiratory function (133–135). These unusual situations highlight the potential benefits of GH replacement in childhood other than linear growth.

GH replacement has evolved since the pioneering work of the 1950s using cadaveric pituitary-derived GH. Numerous studies have helped define the optimal management of GH replacement during childhood. The recognition of the importance of GHD during adult life has necessitated a more detailed study of GHD and the impact of treatment, which has resulted in a reevaluation of pediatric practice. The monitoring of parameters other than linear growth to help refine GH therapy should now be incorporated into childhood GH replacement. Further research will be required to define the optimal management of the transition from pediatric to adult GH replacement, and a smooth changeover will only be accomplished once the benefits of GH after the completion of growth are accepted by pediatric and adult endocrinologists alike.

V. Adult GH Replacement: Historical Perspective

The earliest report of the beneficial effects of GH in the treatment of adult hypopituitarism was in 1962, when increased vigor and well being were reported by a 35-yr-old hypopituitary patient treated with cadaveric GH (136). This was followed, approximately 30 yr later, by a series of randomized, placebo-controlled trials, in which it was convincingly demonstrated that treatment of GHD adults with rhGH led to significant improvements in body composition, well being, and serum lipoprotein levels (1–6). Almost coincident with these studies came the first (137) of several reports (138–140) to suggest that hypopituitarism is associated with decreased life expectancy compared with age-matched healthy controls, despite adequate replacement with glucocorticoids, thyroid hormone, and sex steroids. Although it remains an intriguing possibility that the increased visceral adiposity and abnormal cardiovascular risk profile associated with adult GHD contribute to the demonstrable decreased life expectancy, there are at present no solid data to support this hypothesis or that treatment with rhGH improves mortality outcome in adult hypopituitarism.

VI. Rationale and Strategies for GH Replacement in Adults

In the absence of evidence that GH replacement therapy for adult GHD is associated with an improvement in mortality outcome, it is the development of symptoms of a char-

acteristic clinical syndrome, discussed in detail below, that is the most frequent trigger for consideration of treatment of hypopituitary adults with rhGH. Unlike other hormones used for the treatment of hypopituitarism, for which the benefits of replacement therapy are universally accepted, there is considerable national variation in the clinical indications for the prescription of GH. This variation relates in part to financial constraints, but it is also indicative of an area of clinical practice in which the sudden availability of an unlimited supply of drugs has necessitated a rapid evaluation of the indications for its use and, hence, a strategy for its monitoring. Essentially three main approaches to the practice of GH replacement have been used. One is that because of its cost and the lack of evidence of its long-term efficacy in improving cardiovascular risk and reducing mortality, GH replacement should not be offered to hypopituitary patients A second approach, adopted by some countries, is that all hypopituitary patients with GHD require GH replacement, simply on the principle of complete hormone replacement therapy. In most countries, however, a third approach is adopted involving selection of patients for GH replacement. In the United Kingdom and many other European countries, selection is made largely on the basis of quality of life and/or bone mineral density considerations, but alternative strategies could include selection of patients with a particularly high cardiovascular risk profile.

The potential improvement of several of the adverse features of the adult GHD syndrome with rhGH therapy means, in turn, that changes in these parameters are used as clinical indicators of GH efficacy during replacement therapy. During the double-blind placebo-controlled trials of GH replacement, and in the immediate period after its license for use in adults, it was thought, by analogy with pediatric practice, that clinical monitoring would be sufficient and that markers such as body composition would simply substitute for linear growth. However, with time and shared clinical experience, it has become apparent that individual responsiveness to GH is highly variable and that the dose should be adjusted to suit each individual patient. This, in turn, is accomplished using a combination of tolerability (*i.e.*, the occurrence of side effects), clinical response, and measurement of biochemical indices of GH action. In the debate surrounding the optimization of GH dosing schedules, supportive evidence comes from a combination of placebo-controlled studies (both single- and multicenter) and information collected through international outcomes-based multicenter research databases, in which data are recorded during longitudinal follow-up in a conventional clinical setting. Although patient numbers may be limited in a single center, it is often the case that those patients have been treated by a single physician or group of physicians in an identical manner, such that it becomes possible to draw conclusions about specific treatment protocols. In contrast, dosing strategies vary between centers, but large databases permit the identification of subtle trends regarding individual susceptibility, together with early detection of important safety issues that may not be possible from a single center or even a single country.

VII. Tolerability

rhGH has an identical amino acid sequence to endogenous GH (61), such that side effects of GH replacement therapy are almost exclusively due to excess dosing. In the early trials of GH replacement, symptoms related to the antinatriuretic actions of GH, such as edema, arthralgia, and myalgia, were common and necessitated dose reductions in up to 40% of patients (2, 3). Side effects were more common in elderly and obese patients (141), both of whom would have received disproportionately larger doses, in the early studies using weight-based dosing regimens, than would be predicted from the physiological principles of GH secretion outlined above. Side effects were significantly reduced by beginning GH at smaller doses, building up to the (then) weight-based target dose. Conversely, trials involving mostly lean and young adults have been associated with fewer side effects (142). However, even when GH doses are lowered because of adverse symptoms, biochemical markers of GH action, such as serum IGF-I, remain elevated in up to one-third of patients (143), suggesting that the absence of classical symptoms of GH overtreatment is a relatively crude method of judging excess GH exposure.

VIII. Clinical Response to GH Replacement

In the absence of conclusive evidence that GH replacement reduces cardiovascular mortality, it is the potential reversal of many of the features of GHD, most notably abnormal body composition, impaired quality of life, osteopenia with increased fracture risk, and cardiac dysfunction, that leads to the initiation of treatment. It might therefore be argued that each of these could be used as a marker of efficacy during GH replacement. In discussing the merits of different approaches to adult GH replacement therapy, it is important to note that supportive evidence comes from both placebo-controlled and open-label studies, each of which provide separate, but complementary, information.

A. Body composition

GHD adults have increased android (abdominal and visceral) fat, decreased lean body mass, and decreased total body water compared with age-matched healthy controls (1, 2, 144). Several double-blind, placebo-controlled studies, all slightly different in design, have shown consistent, beneficial effects on all these parameters with GH replacement therapy (1, 2, 3–5), attributable to its known lipolytic (145), protein synthetic (146), and antinatriuretic actions. A variety of techniques are available for the assessment of body composition in clinical trials of GH therapy in adult hypopituitarism, including bioimpedance analysis (147), isotope dilution estimation of total body water (TBW) (148), total body potassium (TBK) estimation using a ^{40}K counter (149), dual energy x-ray absorptiometry (150), anthropometry (151), and CT scanning (152). Although some groups have used a four-compartment model of body composition (144), most studies have monitored changes in body composition on the basis of a two-compartment model [fat mass (FM) and lean body mass (LBM)], each of which has distinct physico-chemical

properties. For example, estimates of LBM from measurements of TBK rely on an assumption of 60 mmol potassium per kg LBM (153). FM is then calculated by subtracting the derived LBM from the total body weight. Isotopic dilution measurements of TBW may be used to calculate LBM on the basis that water constitutes 73% of LBM (hence LBM = TBW/0.73). It is important to note that such calculations are based on models of body composition in healthy, GH-replete individuals and that extrapolation to GHD adults may not be strictly valid. Further, although most techniques measure body fat with accuracy and precision, some techniques, notably bioimpedance analysis and dual energy x-ray absorptiometry, may overestimate LBM changes (154). However, as can be seen from Table 1, the qualitative effects of GH replacement on body composition in adult GHD (both AO and CO) have been strikingly similar in the trials listed, all of which were randomized, double-blind, and placebo controlled. Some of the quantitative differences between studies may, at least in part, be attributed to different GH dosing regimens used and the discrepancies known to exist between the various techniques available for the measurement of body composition (154). Although many of the above techniques are not routinely available outside supervised clinical trials, it should be noted that the simple measurement of waist-hip ratio correlates well with the reduction in visceral FM that occurs with GH replacement and provides a sensitive and reproducible method of monitoring certain aspects of altered body composition during GH therapy (2).

Since the original demonstration, in placebo-controlled clinical trials, that weight-based doses of GH replacement therapy favorably modify various indices of body composition, a number of open-label studies have examined the value of using such changes as the major determinant of dosing during replacement therapy. Johannsson *et al.* (158) randomized 60 patients to one of two dosing regimens of GH: a high dose of 12 μg/kg/d or an individualized dose, in which a low starting dose of GH was followed by individual dose adjustments according to measurements of serum IGF-I and changes in body composition, with relative weighting given to the more abnormal parameter. Dose increments were generally made on account of a serum IGF-I level below the age-related reference range, but in those patients with a normal baseline serum IGF-I, dose adjustments were made according to measurements of body composition. Improvements in body composition were similar in the two groups but, in some individualized dose patients, dose increments on account of persistently abnormal body composition resulted in elevated serum IGF-I levels. This would suggest that, in some hypopituitary patients, attributing the totality of abnormal body composition solely to GHD may not be appropriate and that increasing the dose of GH in an attempt to normalize body composition may result in overtreatment, judged by biochemical markers of GH action.

In a separate study (159), assessments of body composition and measurements of biochemical markers of GH action (IGF-I, IGFBP-1, and BP-3 and ALS) were monitored during 12 months of treatment with a weight-based GH dosing regimen. Significant improvements in body composition were observed. Although no individualized dosing was made on the basis of the above measurements, dose reductions were necessary in 7 of 20 patients because of side effects of fluid retention. Even with these dose reductions, serum IGF-I remained elevated in seven patients (35%), while ALS and IGFBP-3 were above the age-related reference range in five (25%) and three (15%) patients, respectively (159).

De Boer *et al.* (143) conducted a 12-month placebo-controlled trial of GH replacement, randomizing 46 GHD male patients to one of four treatment protocols: placebo for

TABLE 1. Effects of GH on body composition in various randomized controlled trials

First author (yr)	Patients	Duration	Technique	Dose GH used	Observed
Salomon (1989) (2)	24 (AO/CO)	6 months	TBK, AP	0.5 IU/kg/wk ≡ 25 μg/kg/d	LBM ↑ 5.5 kg FM ↓ 5.9 kg
Jorgensen (1989) (1)	21 (CO)	4 months	CT	2 IU/m^2	Quadriceps muscle Quadriceps fat volume
Bengtsson (1993) (3)	10 (AO)	6 months	TBK, CT, BIA	0.25–0.5 IU/kg/wk ≡ 13–26 μg/kg/d	LBM ↑ 4.6 kg FM ↓ 6.1 kg
Johannsson (1996) (155)	68 (AO)	6 months	DEXA, BIA	0.24 IU/kg/wk 12 μg/kg/d	LBM ↑ 2 kg FM ↓ 2.6 kg TBW ↑ 1.6 kg
Attanasio (1997) (156)	97 (AO) 74 (CO)	6 months	BIA, AP	0.25 IU/kg/wk ≡ 12.5 μg/kg/d	LBM ↑ 3.5 kg FM ↓ 4.9 kg (AO) LBM ↑ 3.7 kg FM ↓ 5.5 kg (CO)
Whitehead (1992) (5)	14 (MO)	6 months	AP, CT	0.5 IU/kg/wk ≡ 25 μg/kg/d	LBM ↑ 3.6 kg FM ↓ 2.2 kg
Christ (1997) (157)	13 (MO)	3 months	BIA, IDL	0.25 IU/kg/wk ≡ 12.5 μg/kg/d	LBM ↑ 3.4 kg FM ↓ 2.4 kg TBW ↑ 2.5 kg

AO, Adult-onset GHD; CO, childhood-onset GHD; FM, fat mass; MO, mixed-onset GHD; TBK, total body potassium; BIA, bioimpedance analysis; CT, computed tomography; AP, anthropometry; IDL, isotope dilution; LBM, lean body mass.

6 months followed by GH 2 IU/m^2/d; or one of three doses of GH for 12 months (1, 2, and 3 IU/m^2/d). Some reductions in dose were necessary due to unacceptable side effects of GH excess, but the absence of such symptoms was a poor guide to overtreatment, judged by serum IGF-I levels (Fig. 2). Most of the patients treated with the highest dose of GH had serum IGF-I levels outside the age-related reference range. It should be noted that, in this study, the doses of GH necessary to normalize serum IGF-I were also associated with restoration of normal tissue hydration, emphasizing the potential use of clinical markers of GH efficacy during GH dose titration.

A more global assessment of the effect of GH on body composition and the relationship to serum IGF-I comes from a recent international report of 1,018 patients receiving GH replacement in 20 different countries (160). Improvements in body composition, as determined by the simple measurement of waist-hip ratio, were similar in patients enrolled at the time of initiation of GH (GH "naïve" patients) and non-naïve patients (those already taking GH at enrollment into the database). However, mean GH dose and mean serum IGF-I were significantly higher in non-naïve patients, most of whom had previously been treated with weight-based GH regimens, with subsequent adjustment of dose during clinical follow up. Overtreatment with GH (defined as a serum IGF-I greater than 2 SD scores above the mean) was seen in both groups of patients, but was significantly more common in non-naïve patients (23.3 *vs.* 15.9%). This might suggest that the "extra" GH received by non-naïve patients is not associated with a significant benefit in terms of improved body composition, but is associated with a significantly greater incidence of excess GH exposure, judged by elevated levels of serum IGF-I (160).

B. Quality of life and well-being

Reduced quality of life and sense of vitality are well recognized features of the adult GHD syndrome (161, 162). Although this may in part relate to abnormal body composition and impaired muscle strength, there is widespread agreement that the low energy levels, social isolation, increased emotional stress, impaired socio-economic performance, and greater difficulties forming relationships evident in many hypopituitary patients are directly due to GHD. In many countries, availability of GH is limited to patients with severe GHD associated with one or a combination of these symptoms, and their improvement is therefore an important clinical parameter by which to judge the efficacy of GH replacement. The early trials of GH replacement used a variety of generic methods to measure and monitor well-being such as the Nottingham Health Profile (NHP) (163) and the Psychological General Well-Being Schedule (PGWBS) (164). The NHP questionnaire consists of a number of specific questions, with yes/no responses, about energy levels, sleep, relationships, emotional responses, physical mobility, and pain. The Psychological General Well-Being Schedule (PGWBS) involves the use of a rating (from 0, worst, to 5, best) for a series of questions about affective categories such as anxiety, depression, positive well-being, general health, and vitality.

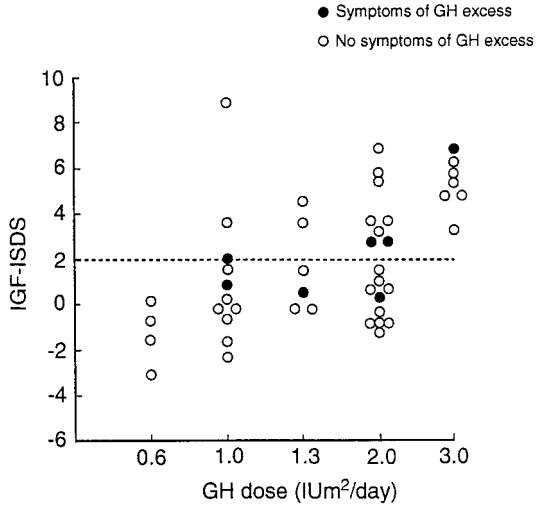

FIG. 2. Measurement of IGF-I response in 46 men with CO-GHD randomized to receive one of three starting doses of GH with subsequent adjustment according to clinical characteristics. ●, Symptoms of GH excess. ○, No symptoms of GH excess. [Reproduced with permission from H. de Boer *et al.*: *J Clin Endocrinol Metab* 81:1371–1377, 1996 (143). © The Endocrine Society.]

A number of placebo-controlled studies have documented statistically significant improvements in well-being, assessed by various methods, after the initiation of GH replacement (3, 162, 165), although such results have not been universally reported (5, 166). The reasons for such discrepancies are not entirely clear, although it is interesting to note that many patients in the study of Baum *et al* (166) did not achieve significant increments in serum IGF-I levels, suggesting that compliance with GH therapy may have been suboptimal. It is also important to note that patients who participated in the early trials of GH therapy were frequently the most severely disadvantaged in terms of psychological distress (167) and therefore more likely to wish to continue with GH replacement after a therapeutic trial (168). Hence, because of these findings, caution should be exercised in the interpretation of psychological well being data.

Since these placebo-controlled studies, a number of open-label studies have examined the clinical utility of using well-being scores as a marker of efficacy during GH replacement. In most cases, these studies have used doses of GH that would now be considered inappropriately high, and the proportion of patients with a serum IGF-I above the age-related reference range was, in some cases, as high as 56% (169). In one study (170), the effect of two different GH dosing regimens (0.012 and 0.024 mg/kg/d) on well-being, judged by NHP and PGWB scores, was investigated. Identical improvements in well-being were observed in both groups, yet 45% of the patients in the higher dose group had an elevated serum IGF-I compared with 24% receiving the lower dose. In other words, the extra GH administered resulted in no greater clinical benefit in terms of well-being, but was associated with biochemical overtreatment in nearly twice as many patients. In the same report, of those patients that chose to continue GH therapy after the conclusion of the trial, 33% had a supranormal serum IGF-I compared with 30% of those who elected to discontinue due to a lack of improvement in well-being. If the dose of GH in the "non-improvers" had been increased because of a poor clinical response, it may have pushed serum IGF-I further into the acromegalic range.

More recently, attempts have been made to use scoring systems for psychosocial morbidity that are more specific to GHD. The adult GHD assessment (AGHDA) score (171–173) provides a sensitive and highly reproducible method of monitoring improvements in the psychosocial consequences of GHD that may accompany GH replacement therapy. The AGHDA questionnaire consists of 25 questions derived from the symptoms most frequently reported by patients with adult-onset GHD. A score of 25/25 represents the worst possible well-being score, while scores of 4/25 or less have been recorded in a normal control population (174). In those patients whose well-being improves with GH, improvements in AGHDA scores occur within 3 months of GH replacement therapy in the majority of patients and are maintained at 6 and 12 months (175). Interestingly, improvements in AGHDA scores may be seen in some patients treated with GH whose dose is insufficient to have caused a significant increment in serum IGF-I, suggesting that improvements in the psychological aspects of GHD may, at least in part, be mediated directly by GH rather than via generation of IGF-I (175). It is not known whether patients exposed to excess GH (either in the context of acromegaly or by overtreatment with GH in hypopituitarism) have AGHDA scores that are different from control populations. However, an interesting comparison can be made between hypopituitary patients treated initially on weight-based dosing schedules, with subsequent dose adjustment during clinical follow-up and patients initially started on low doses of GH with subsequent careful dose titration on the basis of levels of serum IGF-I (175). Maintenance doses of GH and serum IGF-I levels were significantly higher in the patients initially treated with weight-based dosing schedules, yet well-being, as judged by AGHDA score, was no different.

C. Bone density and bone remodeling

It is thought that, in childhood, GH promotes longitudinal bone growth by a combination of a direct effect on epiphyseal chondrocytes (176) and by paracrine generation of IGF-I (177). However, it is now widely accepted that GH also has an important role to play in the achievement of peak bone mass after the completion of linear growth and also in the maintenance of bone mass through adult life. AO hypopituitary patients receiving conventional endocrine replacement therapy are osteopenic compared with age-matched healthy controls (178, 179), an observation that is almost certainly clinically relevant given the increased fracture rate evident in this patient group (180). Furthermore, there are data to suggest that the severity of bone loss is proportional to the biochemical severity of GHD (181). The mechanisms for this disadvantage are not fully understood but are likely to relate, at least in part, to reduced bone remodeling activity. Activity of the bone remodeling unit (*i.e.*, the rate of bone turnover) may be assessed by measuring markers of the activity of the two limbs of the bone remodeling unit. Osteoclasts mediate bone resorption, and indices of their activity include pyridinoline, deoxypyridinoline, and serum type I carboxy-terminal cross-linked telopeptide. Markers of osteoblastic activity (bone formation) include the bone-specific isoenzyme of alkaline phosphatase (BSAP), osteocalcin, and carboxy-terminal propeptides of type I collagen. GH stimulates proliferation and differentiation of osteoblasts *in vitro* in humans (28) and in mice (182) and further, surrogate, evidence for an important effect of GHD *in vivo* is supported by the observation of subnormal levels of osteocalcin and BSAP in adults with GHD (142, 183).

Although osteopenia is an important factor in considering a trial of GH replacement, few clinicians would regard it as the sole reason to begin treatment. However, changes in BMD represent an important marker of efficacy of GH therapy, and a review of the data in this regard is appropriate. A number of placebo-controlled trials have examined the effect of GH replacement on bone metabolism and BMD. From these studies it is apparent that GH replacement is frequently associated with a reduction in bone density in the short term (184–186), probably as a result of an expansion of the bone remodeling space (186). However, with more prolonged treatment increases of bone density of 4–10% above baseline, measurements have been recorded (185, 187). The study of Baum *et al.* (187) is particularly noteworthy as the increments in BMD were achieved with a dosing regimen of GH that specifically aimed to avoid overtreatment by maintaining serum IGF-I levels within the age-adjusted normal range. The timescale over which these changes occur clearly preclude placebo-controlled studies of the long-term effects of GH on BMD, but a number of open-label studies suggest that the increments in BMD above baseline that are evident in placebo-controlled trials continue with more prolonged GH replacement therapy over several years (142, 188, 189).

An earlier indication of the efficacy of GH replacement on bone than that evident by changes in BMD is provided by measurement of markers of bone resorption and formation. Several placebo-controlled studies have documented significant increases in markers of bone metabolism as early as 4 months after beginning GH (190), possibly earlier (189). From these and other reports it is clear that individual response is highly variable and that measurement of markers of bone metabolism have little use outside the setting of a clinical trial. Furthermore, there is increasing evidence that the response to GH in terms of BMD is, in part, gender dependent (189, 191). In men, prolonged GH replacement is associated with sustained increments in BMD, whereas in women the benefits appear to be limited to a stabilization of bone density. In both of these studies serum IGF-I was maintained within the age-related reference range, although the GH doses used were higher in women, further emphasizing the need for individualized GH dosing.

Although, as stated earlier, osteopenia is seldom the sole reason to initiate GH replacement for adult hypopituitarism, the timescale of the effect of GH on BMD is such that a cautionary review of the potential effects of overtreatment is appropriate, particularly as most of the studies reviewed above used unphysiological, weight-based doses. GH excess in the context of acromegaly is associated with elevated serum levels of osteocalcin (192), changes that are similar to those seen in many of the studies of GH replacement on bone and which are corrected by successful surgical and/or medical treatment (192, 193). When not associated with hypogonadism, acromegaly is also associated with increased bone mass and density, periosteal growth, and bone widening

(194). Hence, it seems prudent for patients with GHD and low bone mass who are treated with GH to have their BMD monitored at intervals during therapy, starting around 12–18 months after the beginning of GH therapy. Increments in BMD can be anticipated in most patients, and maintaining serum IGF-I levels within the age-related reference range is likely to avoid the potential adverse consequences on bone of excess GH exposure.

D. Cardiovascular risk factors and cardiac structure and function

The association of hypopituitarism with increased mortality has directed attention to a possible role of GH in the regulation of various cardiovascular risk factors. However, independent of this and the possible role for GH replacement in favorably modifying an individual's cardiovascular risk profile (see *Section XII.A*), there is some evidence that GH improves cardiorespiratory function and exercise performance in hypopituitary adults. This aspect of GH replacement has not been the subject of such intensive research as, for example, the effects of GH on body composition and quality of life. Furthermore, it may be difficult to separate the direct effects of GH therapy on exercise performance and cardiac dimensions and function from secondary effects consequent upon changes in body composition, cardiac afterload, and sodium and water balance associated with GH therapy.

Nass *et al.* (195) demonstrated, in a placebo-controlled trial, that GH therapy was associated with improvements in maximum oxygen uptake and exercise capacity, in the absence of any significant change in cardiac structure, as determined by transthoracic echocardiography. More recently, Woodhouse *et al.* (196) showed that GH replacement improved submaximal exercise performance and was associated with an increase in type I skeletal muscle fiber size, benefits that persisted after discontinuation of GH at the conclusion of the study. No significant change was observed in quadriceps strength, although improvements have been documented in muscle strength in a separate, open-label study of longer duration (197).

The relative contribution of a change in cardiac function to the improved exercise capacity associated with GH therapy is difficult to assess. Indeed, the role of GH in the regulation of cardiac structure and function in adult life is far from clear. Several indices of cardiac structure and function (exercise capacity, left ventricular wall thickness, and fractional shortening) are abnormal in GHD adults compared with age-matched healthy controls (198). This is most striking in patients with childhood-onset GHD, in which there is echocardiographic and radionuclide evidence of reduced cardiac output and impaired diastolic function (142, 199). Evidence for similar abnormalities of cardiac function in adult-onset GHD, however, is rather conflicting. There is little doubt that the documented abnormalities are less marked (198), although this may simply reflect the duration of GHD at the time of study. GH replacement in hypopituitary adults has been associated with an increase in LV wall thickness, stroke volume, fractional shortening, and diastolic function, as measured by prolonged isovolumic relaxation time and early/atrial peak velocity ratio (E/A ratio) in open-label studies of GH replacement (198, 200), but has not conclusively been shown in placebo-controlled trials. Furthermore, in those open studies, individual response to a uniform (weight-based) GH treatment regimen was extremely variable. Although this aspect of GH replacement certainly merits further investigation, the current literature does not overwhelmingly support decreased cardiovascular performance and exercise capacity as an indication for the clinical use of GH. If GH does indeed improve cardiac function, the therapeutic window is likely to be narrow, particularly with respect to the induction of left ventricular hypertrophy (201). GH hypersecretion (in the context of acromegaly) leads to a specific cardiomyopathy in which, after an initial phase of cardiac hyperkinesis, myocardial hypertrophy and diffuse interstitial fibrosis gradually lead to diastolic dysfunction and, ultimately, congestive cardiac failure (201). The detection of subtle signs of left ventricular hypertrophy and impaired diastolic relaxation may be difficult using standard transthoracic echocardiography, particularly outside the setting of clinical trials, where interobserver variation of measurements may be considerable. Treatment protocols that maintain serum IGF-I levels in the age-related normal range are likely to avoid the theoretical dangers of subtle GH excess on cardiac function.

E. Conclusions

It may be seen, from the above discussion, that clinical monitoring is clearly an important part of the practice of GH replacement (a characteristic clinical syndrome is, after all, the most common indication for a trial of GH therapy). However, individual response to treatment with GH is so variable that an apparent lack of improvement in a single clinical parameter may prompt dose increments that result in levels of IGF-I outside the age-adjusted normal range, but which are not associated with symptoms of GH excess. The question therefore arises as to whether long-term elevation of serum IGF-I is acceptable in the context of the treatment of GHD and, further, whether clinical efficacy is compromised by adopting strategies that specifically aim to avoid this.

IX. Is Overtreatment Acceptable in the Asymptomatic Patient?

The relatively recent advent of unlimited supplies of rhGH and its use for the treatment of AO-GHD means that there are no long-term data regarding the effects of an elevated level of serum IGF-I in hypopituitarism. In the absence of such information, indirect evidence must be extrapolated from clinical experience in the treatment of acromegaly, a condition known to be associated with excess morbidity and mortality (202), chiefly from cardiovascular causes and presumed to be on account of the associated insulin resistance, hypertension, and characteristic cardiomyopathy. The issue of insulin resistance deserves particular mention in the light of the recent report of an increased incidence of type II diabetes mellitus among children treated with GH (123). It is not possible to extrapolate directly such data to adult practice, on account of the heterogeneity of the pediatric popu-

lation reported (including, for example, patients with Turner syndrome and chronic renal failure), but, nevertheless, the argument for the avoidance of pharmacological doses of GH would appear to be strengthened by such experience. Recent reports, both from a single center and from an international study, of the effect of more physiological doses of GH in hypopituitary adults, are reassuring (160, 203).

Aside from the issue of avoiding iatrogenic biochemical acromegaly and its theoretical complications, there are epidemiological data to suggest that an individual's risk of developing carcinoma of the prostate (in men) (204, 205) or breast (in women) (206) may be influenced, at least in part, by their serum IGF-I level, with values in the upper tertile being associated with a higher incidence of developing malignant change in those organs. It is important to note, however, that these studies were performed in normal, GH-replete, adults and that it may not be appropriate to extrapolate such findings to the practice of GH replacement in adult hypopituitarism. Nonetheless, it seems prudent to avoid the use of GH doses that are associated with supraphysiological serum IGF-I levels until more data are available in this regard.

X. Biochemical Monitoring of GH Replacement

Concern about the long-term consequences of iatrogenic overtreatment with GH has caused attention to shift in recent years toward the use of biochemical indices of GH action in the treatment of AO-GHD. IGF-I, the tissue effector of many of the actions of GH, circulates as a ternary complex of 150 kDa in association with IGFBP-3 and ALS. All three peptides are known to be GH dependent and, in theory at least, may be considered as potential markers of GH efficacy. Of the three, IGF-I is widely regarded as the most sensitive and the most useful for the purposes of dose monitoring. In the report of De Boer *et al.* (143), several patients in the highest dose treatment group (3 IU/m^2/d) reported side effects of GH excess. Serum IGF-I was elevated above the age-adjusted normal range in a number of these patients, but in far fewer were there supranormal levels of IGFBP-3 and ALS. This would suggest that these latter two peptides are less sensitive markers of GH action during GH replacement than serum IGF-I. This is supported by the data of Drake *et al.* (175) who treated 50 consecutive adult hypopituitary patients with an identical dose titration regimen, with dose adjustments every 4 wk on the basis of measurements of serum IGF-I made every 2 wk. In addition, serum IGFBP-3 and ALS were measured in one-third of these patients, but the results were found to be too variable for routine clinical use (175) (Fig. 3). In that study, "optimum" GH replacement was arbitrarily defined as a serum IGF-I above the median but below the upper limit of the age-related reference range. This was done to allow those patients with severe GHD in association with a low-normal serum IGF-I the maximum opportunity to benefit from GH replacement. Maintenance GH doses, once the serum IGF-I was in the target range, were higher, and the time taken to reach the target serum IGF-I was longer in females than males (median daily dose 1.2 U *vs.* 0.8, median time taken 9 wk *vs.* 4 wk, respectively). Further, the mean increment in serum IGF-I from baseline, once maintenance dose was achieved, was less in females than males, despite the higher dose, confirming their overall decreased susceptibility to GH. In spite of this smaller increment in IGF-I, there was no gender difference in the extent of clinical improvement, as determined by QoL AGHDA and measurement of waist-hip ratio. Importantly, the extent of clinical improvement was similar to that seen in the original trials that used weight-based dosing. Similar findings were reported by Murray *et al.* (207) whose regimen for GH therapy defined "optimum" GH replacement as when symptomatic clinical improvement (judged by PGWB and QoL AGHDA) coincided with a normal serum IGF-I. Together, these studies indicate that the recent use of lower, more physiological doses of GH, in which a major consideration is the avoidance of elevated serum levels of IGF-I, is not associated with a loss of efficacy.

In spite of the above evidence, there remain some important concerns with regard to the simplistic use of serum IGF-I levels as the sole guide to the restoration of normal GH status during replacement therapy. Serum IGF-I levels do not always reflect the true GH status of an individual patient, as demonstrated by the fact that up to 30% of patients with proven severe GHD have serum IGF-I levels in the lower part of the age-adjusted normal range (208). Furthermore, some patients with active, symptomatic acromegaly with mean GH levels above the safe range (*i.e.*, >5 mU/liter) (202) exhibit normal serum IGF-I levels. The discrepancies observed in some studies between GH status, as judged by indices of body composition, compared with serum IGF-I levels, may be, in part, consequent upon the method of administration of GH, as suggested by studies in rats (209). It should also be noted that most blood samples for serum IGF-I measurements are drawn in the early morning. Given that there is a significant diurnal variation in serum IGF-I level with a single subcutaneous nightly GH injection (with a peak in the morning and a nadir at night) (210), it may be that such dosing strategies are associated with a falsely high incidence of supranormal levels of serum IGF-I.

It should also be noted that changes in serum IGF-I levels in response to GH administration to hypopituitary adults persist long after the effects on protein and lipid metabolism (211). Changes in serum IGF-I correlate poorly with changes in leucine and glycerol kinetics, suggesting that restoration of a normal circulating IGF-I does not necessarily imply normalization of normal body composition (212).

XI. Gender Differences in GH Responsiveness

A compelling argument for the use of individualized, as opposed to simplistic weight- and/or surface area-based GH dosing, is the marked difference in GH doses that are required to achieve an equivalent clinical and biochemical response in men and women. The reasons for this discrepancy are not entirely clear, although attenuation of GH action by estrogen is an obvious candidate. In healthy postmenopausal women, administration of estrogen decreases serum IGF-I levels, despite an increase in pituitary GH secretion, and attenuates IGF-I production during an IGF-I generation

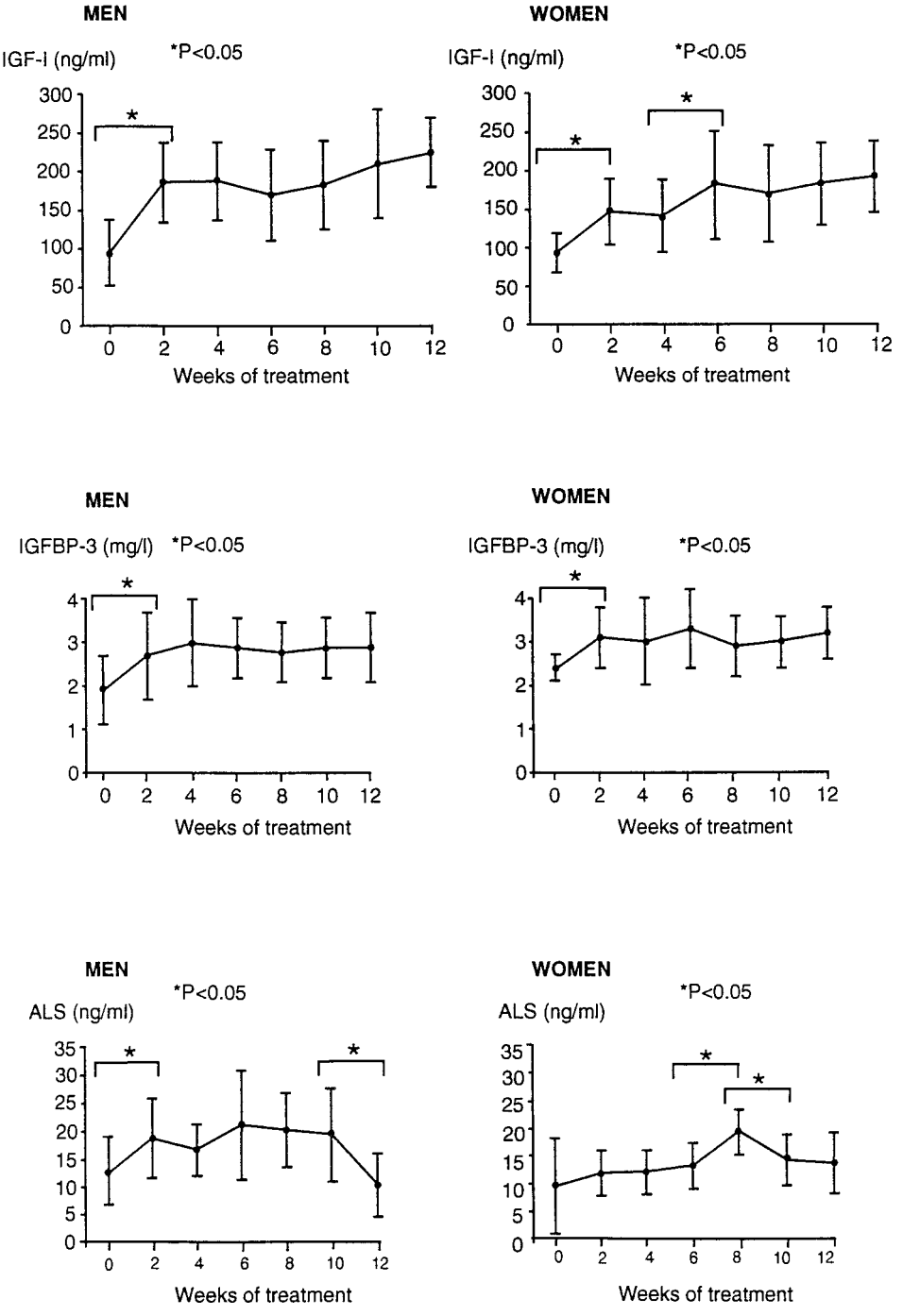

FIG. 3. Serum IGF-I (A), IGFBP-3 (B), and ALS (C) *vs.* time in patients treated by dose titration. Adult GH deficiency assessment (AGHDA) score (D) and waist-hip ratio (E) at baseline and with GH therapy show no difference between males and females, despite higher doses and longer time to reach maintenance dose in females. [Reproduced with permission from W. M. Drake *et al.* : *J Clin Endocrinol Metab* 83:3913–3919, 1998 (175). © The Endocrine Society.]

test (33, 34). Further, oral estrogen administration partially ameliorates the symptoms and signs of acromegaly (31) and, when GH excess is reversed by surgical adenomectomy, the subsequent accumulation of fat mass is more marked in men than women (213). This would imply that estrogen has a modulatory effect on the lipolytic effect of GH, resulting in less marked accumulation of fat when the GH excess is corrected. Clearly, such findings, in healthy and acromegalic individuals, cannot be directly extrapolated to exogenous GH administration to patients with GHD. However, in a placebo-controlled trial, an identical (weight-based) GH dose administered to GHD men and women resulted in a greater reduction in fat mass and serum lipoprotein levels in men compared with women, effects that were accompanied by a statistically greater increase in serum IGF-I levels (214). Recent, open-label studies also support the view that hypopituitary female patients require higher maintenance GH doses than males for a given clinical and biochemical response (175, 215).

The route of estrogen administration has received considerable attention as a possible determinant of maintenance GH dose in hypopituitary women. In healthy, postmeno-

pausal women, transdermal estrogen does not modulate hepatic IGF-I production to the same extent as oral estrogen, although a similar effect may be observed when the number of estrogen patches is increased (33). In an open-label study examining GH doses required to maintain serum IGF-I in the upper part of the reference range, Cook *et al.* (215) demonstrated that women taking oral estrogen required approximately twice as much GH as women taking transdermal estrogen, whose maintenance dose was similar to men. Although other, larger studies have not demonstrated a significant difference in maintenance GH dose on the basis of estrogen usage (160, 175), those studies did not specifically examine the use of transdermal estrogen as a variable. The findings of Cook *et al.* (215) clearly have important implications in terms of the cost of maintenance GH dosing and merit further investigation.

XII. Adult GHD and Vascular Disease

Attempts to unravel the possible mechanisms by which GHD may contribute to the increased mortality of hypopituitarism are severely hampered by the lack of a true control population, *i.e.*, patients with anterior pituitary failure but normal GH reserve. This is because of the predictable way in which hypopituitarism develops, with GHD characteristically antedating failure of gonadotropin secretion and deficiencies in TSH and ACTH reserve. Hence, while it would be logical to compare mortality outcome between patients with hypopituitarism and GHD to those who are hypopituitary but GH replete, the clinical reality is that such patients do not exist. In the absence of a satisfactory control population, observational studies of various surrogate markers of cardiovascular morbidity and their improvement with GH replacement provide some evidence for an etiological role for GH in the increased cardiovascular risk that may be prevalent in hypopituitary patients. These markers include dyslipidemia (156, 216), hyperfibrinogenemia (217), elevated levels of plasminogen activator inhibitor (217), and increased abdominal fat distribution (218). Further surrogate evidence for increased vascular morbidity in hypopituitarism comes from measurements of the structure of and flow in peripheral arteries. Arterial intima-media thickness is a well-validated indicator of early atheroma in epidemiological studies, and observations of easily accessible arteries such as the carotid and femoral correlate well with disease elsewhere such as in the epicardial coronary arteries. The percentage of peripheral arteries containing atheromatous plaques and the number of plaques contained within those arteries are both greater in hypopituitary patients compared with age- and sex-matched controls (219). Measurements of brachial artery and large arterial compliance suggest a reduction in large vessel distensibility (220, 221), but population studies examining whether this translates into significant changes in blood pressure are difficult to interpret on account of the greater medical attention afforded to hypopituitary patients compared with healthy volunteers. GH has both vasodilatory (222) and antinatriuretic (223) actions: hence, the effects of GHD on systemic blood pressure are likely to be complex.

A. GH replacement therapy and dyslipidemia

The effect of GH replacement on lipid metabolism has been studied in several placebo-controlled trials (2, 5, 156, 218). The results of these studies were strikingly similar, with significant decreases observed in serum total cholesterol. Reductions in low-density lipoprotein cholesterol and/or an increase in high-density lipoprotein cholesterol were also observed, although these did not reach significance in all studies. GH replacement appears to have little effect on plasma triglycerides or ApoA levels. Changes in Lp(a) levels, known to be an independent risk factor for vascular disease, high-density lipoprotein cholesterol, and triglycerides have been inconsistent, vary considerably with the assay methodology (224), and may depend, at least in part, on the patient's apoE phenotype (225).

Although these abnormalities and their improvement with GH replacement are frequently cited as evidence that GHD is associated with increased mortality, it is important to note that many of these studies used weight-based dosing regimens that would now be regarded as excessive (0.25 IU/kg/wk, 12/5 μg/kg/d, with the exception of one study (2) in which twice this dose was used). Such concerns apply equally to other surrogate markers of increased cardiovascular morbidity such as hyperfibrinogenemia (217) and elevated levels of plasminogen activator inhibitor (217). In a recent open-label study of the effects on lipid profiles of GH replacement delivered by dose titration to maintain serum IGF-I above the median but within the age-adjusted normal range, statistically significant reductions in total cholesterol and LDL-cholesterol were evident (203). However, the changes were lower than those observed in the original placebo-controlled trials, and the greatest benefit was seen in patients with the highest values at baseline. Abs *et al.* (160) reported that, since the advent of dose titration, the use of more physiological doses of GH has been associated with only modest improvements in lipid profiles in males and little change in females. These reports emphasize that it is not possible to extrapolate data from studies utilizing pharmacological doses of GH to modern clinical practice in which lower, more "physiological" doses are used; and that it is far from clear whether GH replacement invariably improves the cardiovascular risk profile of patients with GHD.

XIII. Alternative Mechanisms for Accelerated Vascular Disease

Aside from GHD, unphysiological hormonal replacement is another possible cause of accelerated atherogenesis. Many features of glucocorticoid (GC) excess (glucose intolerance, central obesity, hyperinsulinemia, and raised triglycerides) are similar to those of hypopituitarism with GHD and known to be associated with increased vascular disease (226, 227). GC monitoring regimens vary significantly between centers, but measurements of circulating cortisol in patients taking hydrocortisone generally suggest excess GC exposure during the day and underreplacement at night (228, 229). Further, metabolism of cortisol to inactive cortisone is GH dependent (230, 231), such that administered hydrocortisone may remain metabolically active for longer in GHD subjects.

The long-term effects of prolonged overnight hypoadrenalism on atherogenesis are unknown.

There is evidence that subclinical primary hypothyroidism is associated with accelerated atherogenesis (232). This risk, although somewhat attenuated, may extend to individuals with compensated hypothyroidism associated with dyslipidemia. Biochemical assessment of thyroid function in hypopituitarism is restricted to measurement of circulating T_4 and T_3, levels of which may vary by at least 2-fold in healthy subjects. It is therefore difficult to be certain that subtle underreplacement with thyroid hormone is not an etiological factor for premature vascular disease in hypopituitarism. Conversely, given the recent demonstration of increased cardiovascular morbidity associated with a low TSH (233), it is equally difficult to be sure that marginal overreplacement is not contributing to increased cardiovascular mortality.

In summary, it is now accepted that AO-onset hypopituitarism is associated with reduced longevity. The relative contribution of premature vascular disease to this increased mortality has not been consistent, but there is a substantial body of indirect evidence that hypopituitary patients have an unfavorable cardiovascular risk profile. The extent to which GH replacement corrects this adverse risk profile is not clear, because many studies have used pharmacological rather than physiological doses of GH. Data from a large, multinational outcome-based research database suggest that fasting lipid profiles are significantly improved by the lower doses of GH now considered to be more appropriate for replacement, although the effects are less dramatic than those observed in the early placebo-controlled trials (160). It will require several more years of large-scale surveillance to determine the net effect of GH on cardiovascular morbidity and mortality in hypopituitarism.

XIV. Transition from Pediatric to Adult Clinic

The completion of linear growth has, traditionally, been the logical endpoint at which to discontinue GH therapy for GHD children. Indeed, for many patients, particularly those with isolated GHD, this is likely to have been predicted by the child's physician at the start of treatment. However, in the light of the above discussion on the effects of GH in adult hypopituitarism, the practice of discontinuation of GH at final height requires careful reevaluation. Adults and children with GHD have traditionally been managed by physicians in separate departments, and the clinical research performed by those departments has, in general, focused on different clinical endpoints. This means that there is a paucity of data on which to base management decisions in young adults who have completed their linear growth. As discussed earlier, GH secretion rates decline rapidly once puberty is complete and continue to decline steadily thereafter (39). Hence, the diagnostic criteria for severe GHD in adults (<3 μg/liter, 9 mU/liter during a provocative test) (234) may not be appropriate for an individual who has just completed linear growth. The definition of severe GHD in this age group has yet to be defined, but it is likely to be more closely allied to the pediatric range (<5–10 μg/liter, <15–30 mU/liter) (235).

Observational discontinuation studies provide some surrogate evidence as to the effects of GH discontinuation at the completion of linear growth. Such studies require cautious interpretation, because of the fact that a substantial proportion of patients treated with GH replacement in childhood show evidence of normal GH status by the time final height is achieved (236–240). This observation makes retesting mandatory before re-starting GH can be considered. The guidelines from a consensus meeting on the diagnosis of GHD in adults (7) suggested that in patients with isolated idiopathic GHD, two biochemical tests of GH status are required, while a single provocative test is sufficient in patients with multiple pituitary hormone deficits. The issue is further clouded by the fact that, until fairly recently, supplies of GH were limited, such that some of the older publications in which GHD adolescents have been compared with age-matched healthy controls may have included patients treated with suboptimal GH dosing regimens due to the lack of availability of pituitary-derived GH.

XV. Effects of Discontinuation of GH Treatment at Final Height

It is not sufficient merely to cite evidence from the adult literature as an argument for continuing treatment with GH in GHD adolescents after the completion of linear growth. Several observations, such as lower IGF-I levels, lower lean body mass, reduced height, less reduction in quality of life assessment, and less marked derangement of serum lipoprotein levels in CO-GHD, suggest that the CO- and AO-GHD states should be considered as two separate entities (156). Given that the logic for continuation of GH into adult life lies in the prevention of the adult GHD syndrome, a brief review of the evidence that withdrawal of GH therapy in this patient group is associated with adverse pathophysiological changes is necessary before possible dosing strategies can be discussed.

A. Body composition

There is some evidence, in GHD young adults, that withdrawal of GH therapy is associated with adverse changes in body composition. Rutherford *et al.* (241) reported a statistically significant decrease in muscle strength and an increase in fat mass in adolescent patients with CO-GHD 1 yr after cessation of GH. Similar changes in fat mass were subsequently reported by Colle and Auzerie (242) and, although, both studies were small (eight and six patients, respectively), analysis of nine separate studies that have examined this question does suggest that withdrawal of GH at the completion of final height is associated with the development of abnormal body composition (243). In a recent report of the effects of discontinuation of GH at final height (244), adverse changes in body composition within 12 months of withdrawal of GH were documented, in patients subsequently shown to be GHD on retesting at the conclusion of the study. However, interpretation of these data is made difficult because IGF-I levels in those patients subsequently shown to have persisting GHD were approximately 50% greater than those with normal GH reserve on retesting. In other words, such data may relate more closely to the effects of the reversal

of GH excess than to the discontinuation of more physiological doses of GH.

In a recent study, Vahl *et al.* (245) randomized patients either to continue with a weight-based GH dose or placebo for 12 months after the completion of linear growth. At the end of this time, all patients continued GH. Statistically significant increases in body fat were noted in the placebo-treated patients, changes that were, in large part, reversed when GH was recommenced. Interestingly, despite these changes in body composition, no significant differences were noted in insulin sensitivity between the two groups (246). These findings provide important, complementary evidence to observational discontinuation studies, but must be interpreted with a degree of caution. The (weight-based) doses of GH used in the study were closer to those employed in pediatric than adult practice, despite the fact that several of the patients were in their mid-20s. Serum IGF-I levels were elevated in several patients at the start of the study and remained elevated in many of those randomized to continue GH. Studies in similar patients, utilizing lower, more physiological, doses of GH, are needed.

B. Bone mineral density

As discussed earlier, there is clear evidence that GH is important for the maintenance of BMD in adults, and it is likely to be important in accruing bone mass early in life (179, 247). Most bone mass is acquired during late adolescence or young adulthood and, together with subsequent age-related loss, determines an individual's fracture risk later in life. Patients with CO-GHD are relatively osteopenic compared with age-matched healthy controls (179, 247). This is true both for patients with isolated GHD and those with multiple pituitary hormone deficiencies (247), supporting a role for GH in the attainment of peak bone mass. After cessation of GH therapy in young men with AO-GHD, far from significant bone loss, BMD continues to increase for at least the next 18 months (248), although it remains unknown whether this increase in bone mass is suboptimal in the absence of GH replacement. However, the confounding issue of the adequacy of GH treatment may be particularly important in this area, as BMD is significantly higher in younger patients treated with rhGH compared with patients treated initially with cadaveric GH (249). Although it is generally accepted that GHD in childhood is associated with a failure to reach peak bone mass, there are no data at present from controlled trials to justify a recommendation of continuation with GH therapy at final height. However, it is clear that BMD should be assessed in these patients and, indeed, continuation of GH therapy until the achievement of peak bone mass has been advocated (249).

In summary, there is some evidence that withdrawal of GH therapy on completion of linear growth in GHD adolescents may be associated with impaired somatic development and adverse changes in body composition. To date, there is little evidence that such patients are significantly disadvantaged in terms of quality of life and well-being, insulin sensitivity, or surrogate markers of cardiovascular risk. In the absence of such data to justify widespread continuation of GH into adult life and the paucity of evidence of the consequences of delaying reintroduction of therapy, a number of potential strategies exist. One approach is to continue GH therapy in a seamless manner into adult life with only a brief cessation of therapy to allow reassessment of GH status. A second strategy, given that the greatest short-term benefit of GH replacement in adult life is improved quality of life and that psychological benefit is proportional to the degree of pretreatment morbidity, is to offer GH replacement only to those patients who, on withdrawal of GH at final height, are most disadvantaged in terms of QoL. A proportion of GH-deficient patients report entirely normal QoL while off treatment, and this is more common in CO disease (156). Hence, a period of time off treatment would allow an assessment of whether GH therapy is likely to be symptomatically beneficial. A policy of seamless transition from childhood to adulthood would not permit the identification of such patients. Furthermore, the prospect of life-long therapy with GH may not be particularly appealing to an adolescent patient who has completed treatment to final height. Compliance with further therapy is likely to be greatly enhanced if the patient is allowed to experience a significant period of symptomatic GHD before beginning replacement in adult life. A third strategy for the management of GH during transition to adult life is to continue with GH for a few years after the completion of growth to facilitate the development of peak bone mass, after which therapy could be discontinued.

XVI. Dosing Strategies for the Adolescent Patient

In addition to the timing of GH therapy during transition from childhood to adult life, a question remains regarding the most appropriate dose to employ. The doses of GH used toward the end of linear growth are approximately 3–6 times the average dose used in adult GH replacement. This is in keeping with the decline in normal GH secretion after the completion of puberty. A number of different approaches may be taken to dosing in such patients, and the most appropriate method will depend, at least in part, on the timing of the recommencement of GH after retesting. If GH therapy were stopped for a number of years after the attainment of final height, restarting treatment at a low dose and gradually titrating up according to the IGF-I response (*i.e.*, the increasingly standard practice in adults) would probably be most appropriate. However, if a seamless transition of GH therapy into adult life is used, various, alternate, options exist. A low-dose titration regimen could be instituted as soon as the decision has been made to continue treatment. However, it is likely that the dose required to normalize serum IGF-I levels in the period immediately after the completion of linear growth will be closer to the pediatric than adult dose, and building up to an appropriate maintenance dose may take some time. It may therefore be more appropriate initially to continue treatment at the pediatric dose and gradually titrate down according to serum IGF-I levels. A further potential approach would be to continue GH at the higher pediatric dose until the completion of somatic development to allow maximal accrual of bone and muscle mass before transition to adult replacement levels. There are no current

data that indicate the correct approach to adopt although current studies are addressing this issue. Regardless of the strategy adopted, robust age-related reference ranges for GH-dependent serum markers are mandatory.

XVII. Influence of Adult GH Replacement Studies on Pediatric Practice: Reevaluation of Pediatric Practice

It may be considered a disadvantage of adult GH replacement that there is no easily definable clinical endpoint of treatment, such as linear growth, against which therapy can be titrated. However, the absence of an easily measurable effect of treatment has necessitated a far more detailed study of GH replacement that has widened our knowledge of the regulation and actions of GH in adult life. This has also been assisted by the much wider scope for clinical studies in adults compared with children. Placebo-controlled studies are extremely difficult to perform in pediatric practice, particularly when there is only a finite window of opportunity for growth to occur. In addition, assessment of some parameters such as BMD and quality of life in children is problematic. Thus, the extension of GH therapy to adults has provided new information that has prompted a reassessment of pediatric practice and raised a number of important questions.

The results of retesting patients treated for GHD during childhood have demonstrated that a significant proportion have normal GH responses to provocative tests after the completion of linear growth (65, 236). It has been suggested that this may indicate that GHD can be temporary, but no convincing evidence for this theory has been produced. A more likely explanation is that a significant proportion of children diagnosed as GH deficient in childhood actually have normal GH reserve. While the proportion of individuals inappropriately labeled GH deficient will vary between different cohorts (groups with more organic GH deficiency are likely to have fewer patients with normal GH reserve) (236), on retesting it is likely that all large groups of GH-deficient children will contain some GH-replete patients. This has implications for the interpretation of data from studies of childhood GH replacement. The peak GH response to provocative tests negatively correlates with final height in GH-treated children, suggesting that GH-replete subjects will not respond as well to GH replacement as severely GH-deficient patients. This is supported by the observation that GH treatment of children with idiopathic short stature, Turner syndrome, or skeletal dysplasia (all of whom have normal GH secretion), does not result in the same magnitude of growth response as treatment of severely GH-deficient children. Thus, the presence of GH-replete subjects in a cohort of GH-deficient children will dilute the observed response to GH therapy, and studies of GH replacement may therefore be underestimating the benefit of treatment if they contain a significant proportion of normal individuals. In addition, data from treatment of children with idiopathic short stature and Turner's syndrome suggest that larger doses of GH are required to enhance growth of GH-replete children. Clinicians need to be aware of these possible flaws in previous studies and of the potential problems with diagnosis of GHD in childhood.

Studies of the treatment of GH-deficient adults have demonstrated the wide range of actions of GH and have indicated the potential abnormalities associated with GHD and the changes that occur with GH replacement. This has confirmed that the benefits of GH replacement during childhood extend beyond linear growth and suggest that the assessment of parameters other than height may be useful. The efficacy of GH therapy in childhood has, however, been almost entirely evaluated by changes in linear growth. Decisions regarding the selection of patients for GH therapy, the dosing schedules used, and the duration of treatment are based, to a great extent, on auxological criteria, and achievement of a maximal final height is the ultimate (and in some cases the only) goal of therapy. Indeed, a recent commentary on the use of GH for short children over the last four decades focused almost entirely on linear growth (87).

There is, however, a flaw in concentrating only on linear growth when considering the optimal treatment of GH-deficient children. Studies in non-GHD children given GH therapy for idiopathic short stature or Turner syndrome have demonstrated that pharmacological GH treatment results in increased growth velocity and an improvement in final height in GH-replete individuals if enough GH is given and treatment is initiated at an early enough age. This is, of course, no surprise given the increased linear growth observed in children with pituitary gigantism. Thus, excessive replacement of GH-deficient patients may confer a minor growth advantage over physiologically replaced individuals. Complete reliance on growth parameters to monitor therapy is therefore likely to result in overtreatment of some patients. It could be argued that it is more important to maximize the final height of a GH-deficient child than to attempt to achieve near-physiological GH replacement. This is contrary, however, to standard practice in other areas of endocrinology in which physiological replacement of a deficient hormone is usually considered the ideal of therapy. With modern treatment protocols, the majority of GH-deficient subjects will reach a height within the normal range, and it must be questioned, therefore, whether supraphysiological treatment can be justified on clinical or financial grounds.

Finally, the reliance on final height as the ultimate goal of therapy ignores the fact that moderate short stature *per se* does not confer any physical disadvantage on patients. Rather, it is assumed that short stature has a deleterious effect on psychosocial functioning, for which there is some evidence (250, 251). More recent reports, however, have failed to confirm this (252–255) and have suggested that the original studies were flawed by referral bias, as short children with academic or behavioral problems were more likely to be referred to clinics and were therefore more likely to participate in studies than children with short stature who did not have such difficulties (256). Studies of nonreferred populations have failed to show any psychosocial disadvantage in normal short children (257), suggesting that social and behavioral problems may have been inappropriately attributed to short stature. Thus, while there is evidence of psychosocial disadvan-

tage among GH-deficient patients, the extent to which this can be attributed to short stature *per se*, and therefore the extent to which improvements in final height will be beneficial, is doubtful.

There are very few data concerning the impact of GH status on parameters other than growth, such as body composition, BMD, and lipids during childhood. This relates, in part, to the paucity of normative data for comparison in younger subjects, and the difficulties presented by the impact of linear growth and pubertal development on BMD and body composition measurements, particularly in GH-deficient patients in whom poor growth and delay in pubertal development may be apparent. A few studies, however, have demonstrated reduced BMD in GH-deficient children compared with age- and sex-matched normal controls, with improvements after the initiation of GH replacement (249, 258, 259). Despite this, studies in young adults have demonstrated low bone mass after GH replacement in childhood (179, 247, 260, 261). This is likely to be a result of periods of untreated GHD either before the start of childhood treatment or between the completion of childhood therapy and the assessment of bone mass, although the possibility of suboptimal childhood GH replacement also exists.

Changes in body composition are well recognized effects of GH replacement during childhood, although this has rarely been formally assessed. An increase in lean body mass with an associated reduction in fat mass has been demonstrated following commencement of GH therapy (129, 258). After discontinuation of therapy at the completion of linear growth, unfavorable changes in body composition occur within the first 12 months (244). Similarly, beneficial effects on lipid profiles have been observed during childhood GH therapy (258), with adverse changes occurring after the completion of treatment in adolescence (242). Measurement of some of these parameters during childhood will assist in defining an individual's response to therapy. This will be of particular importance at the end of linear growth and may be helpful in deciding the optimal management strategy during the transition to adulthood.

Studies of GH replacement in adult life have also provided information regarding the correct replacement dose for GH-deficient patients. Symptoms of GH excess are relatively more common during the treatment of adults (262), particularly in the initial studies of adult GH replacement in which patients were commonly given supraphysiological doses. In addition, with potentially life-long treatment, some concern exists about the health risks, and extra financial burden, of mild overtreatment. This has been emphasized by recent reports linking circulating IGF-I levels in the upper part of the normal range with breast and prostate cancer in normal individuals (204–206). As a result, efforts have been made to ensure that GH is administered in a physiological fashion, and methods for optimally monitoring therapy have been investigated (143, 263, 264). In adults, measurement of serum IGF-I appears to be the most reliable way of assessing the appropriateness of GH dose, and this, in combination with clinical evaluation, forms the basis for the monitoring of therapy (7).

In pediatric practice, the dose of GH is usually calculated according to weight or surface area, and the appropriateness of this dose is not monitored biochemically. This does not allow for any interindividual variability in GH sensitivity or residual GH secretion. Unfortunately, there are few data regarding IGF-I levels in children treated with GH; a pathologically low level while on treatment implies poor compliance or suboptimal dosage (78), but the fear that many children might only achieve an increase in growth velocity at the expense of a pathologically elevated IGF-I level has not been born out in practice (77, 78), although more data are required. Thus, it is likely that some children treated with GH are receiving supraphysiological doses. Because of the relatively short duration of treatment during childhood compared with that potentially used in adult practice, concerns regarding side effects of mild overtreatment are less. There are no data, however, that confirm the long-term safety of mild GH excess during childhood. In addition, the financial restraints imposed on most practices would argue for using the lowest efficacious dose possible. Thus, it would seem reasonable to aim for physiological replacement as an ideal goal of therapy. Extrapolation from adult practice would suggest that maintaining the IGF-I within the normal range is the most reliable way of achieving this, and monitoring of IGF-I levels during treatment would provide a relatively simple method of individualizing GH replacement. However, there is likely to be some reluctance to rely entirely on the IGF-I level as the indicator of optimal treatment dose in patients who have responded well to GH replacement in terms of growth but demonstrate a high level of IGF-I. There are no data at present that indicate whether reducing the dose to that which will maintain the IGF-I within the normal range would have any deleterious effect on growth. For the time being, linear growth remains the main goal of childhood GH treatment. The usefulness of knowing the IGF-I level in terms of titrating the GH dose remains to be proven in pediatric practice.

Finally, the demonstration of the benefits of GH in adult life suggest that, instead of being a treatment that is confined to childhood, GH replacement should be considered potentially as life-long. The management of the transition between pediatric and adult GH replacement remains a challenge. Preparation for the possibility of treatment in adult life should begin during childhood with discussions of the possible need for continuation of therapy after the completion of linear growth. The most appropriate management of the transition period will depend, to a great extent, on the patient's reaction to the possibility of the continuation of treatment, and this in turn will depend on the information provided by the pediatrician during childhood therapy. A patient who has been assured that GH injections need only be continued until the completion of linear growth is less likely to be receptive to the idea of continuing therapy into adult life than the patient who has been adequately prepared. Thus, the acceptance of treatment during adulthood will be determined, to some extent, by the acceptance of the benefits of adult GH replacement by pediatricians. This will require recognition that there is more to GH replacement than growth itself.

Acknowledgments

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