Clinical Endocrinology

Short Stature and its Treatment*

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The axiom that diagnosis must precede treatment holds true for the management of short stature. What matters is the current rate of growth and the potential for further growth; it is essential to measure accurately the rate of gain in height and the radiological bone age. Early detection of subnormal rate of growth can lead to prevention of dwarfism, but a dwarf with epiphyses closed is beyond remedy.

A child's rate of gain in height is determined by genetic factors that require a benign internal environment for their full expression. No form of therapy can alter a genetically determined height velocity; treatment is possible if an adverse internal environment can be corrected. Smith[1] gave an excellent account of the various forms of dwarfism, including the many eponymous genetic syndromes. The genetic short stature of atypical Turner's syndrome may not be recognized unless the karyotype is known from chromosomal studies. A more common difficulty in diagnosis is the normal slow-growing short child of short parents; the normality is obvious only if the child's height is corrected for parental height, using the data of Tanner *et al.*[2]

Any prolonged illness creates an adverse environment that slows the rate of gain of height. In the same way cyanotic congenital heart disease, chronic hepatic or renal failure, and uncontrolled diabetes mellitus stunt growth. Deficient food intake or absorption are more easily rectified causes of subnormal rate of gain of height. The dietary intake, both in quantity and quality, must be discovered. Steatorrhoea may present as short stature with minimal symptoms referable to the gut. The curious phenomenon of low height velocity due to emotional deprivation[3] is difficult to separate from the nutritional stunting that may affect such unfortunate children. Obviously successful treatment of short stature depends on identifying and removing these adverse environmental conditions.

Endocrine causes of subnormal height velocity are not common. Primary thyroid failure severely limits statural growth and may not be immediately apparent. Adequate tests of thyroid function are always required in assessing growth failure. It is also difficult to distinguish primary from secondary failure of the thyroid due to pituitary lesions. Pituitary function is modified by primary thyroid failure and the secretion of growth hormone is diminished. Therefore, it is not possible to obtain an accurate measure of the pituitary's capacity to secrete growth hormone unless the level of circulating thyroid hormone is normal. That glucocorticoid excess can seriously diminish height velocity is well known from the study of Cushing's syndrome in children and from the many examples of systemic steroid therapy for non-endocrine disease. It is not so widely appreciated that the amount of glucocorticoid required to stunt growth is only a little above normal requirements. Therefore, it is of the utmost importance to keep steroid dosage to the minimum or to consider the use of minimal quantities of corticotrophin.

The role of anabolic steroids in growth in stature is confined to the puberty growth spurt. Failure to mature sexually and to grow as fast as their contemporaries is a common complaint among boys who have achieved normal childhood growth. The success of anabolic steroid or androgen therapy in these cases is not an argument for their use in childhood. At all times the rate of bone maturation exceeds that of the increased height velocity so that it is doubtful if anabolic steroids ever increase the height to a level above that which would eventually be reached without therapy. The use of such steroids should be confined to inducing a puberty growth spurt.

In terms of physiology, diagnosis, and treatment the influence of pituitary growth hormone is of paramount importance and requires full consideration in any discussion of subnormal height velocity and its correction.

Diagnosis of Growth Hormone Deficiency

For much of the time the normal plasma levels of immunoassayable growth hormone are as low as they are in hypopituitarism and the normal transient peaks are as high as the persistent levels of active acromegaly. Consequently growth hormone deficiency can be detected only when little or no growth hormone can be found in the plasma under conditions that provoke maximal growth hormone secretion in the normal person. Many of these conditions (see Table I) have been standardized in formal provocative tests, but in children fear is a dominant stimulus and planned provocation may produce no higher level of plasma growth hormone.

TABLE I—*Substances Stimulating HGH Secretion*

Arginine infusion
Bovril
Early sleep
Exercise
Fear and stress
Glucagon
Hypoglycaemia
Protein feed
Starvation
(Glucose depresses then stimulates)

It is essential to use provocative tests to demonstrate growth hormone deficiency, but the finding of only one high level will prove that no deficiency exists. A greed for more data should not allow the physician to forget the distressed child. The hormone is, of course, measured in terms of its antigenicity rather than its biological potency and the stimuli are concerned with its role as a regulator of energy balance and not as a promoter of growth. Fortunately, Tanner *et al.*[4] have shown

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that there is a direct correlation between the peak values of plasma growth hormone in people with varying degrees of growth hormone deficiency and their rate of growth in height. Exactly what constitutes a subnormal peak value of plasma growth hormone is still a matter of debate and laboratory differences. Partial, as distinct from total, deficiency of growth hormone undoubtedly exists. Most authorities would agree that values of zero are obviously abnormal and that values of 20 ng/ml are normal. Probably values of 10 ng/ml, or less represent partial deficiency.

Preparation of Human Growth Hormone (HGH)

The preparation of HGH for clinical use should satisfy the criteria listed in Table II.

The method of Mills *et al.*[5] is by far the best for obtaining clinical grade HGH, while preserving other pituary hormones for later purification (see Table III). It is essential that each batch prepared should be bioassayed as bulk powder and again when in ampoules. Neglect of this precaution has led to the use of inactive material.

TABLE II—*Criteria for Preparation of Clinical Grade HGH*

(1) Uses stored cadaveric pituitaries
(2) Effective for large batch of glands
(3) Removes other pituitary hormones. (Preferably allowing their individual extraction)
(4) Preparation has minimal antigenicity
(5) Maximum yield of active material more important than chemical purity

TABLE III—*Methods of Preparing HGH*

	Glands per batch	Yield per gland (mg)
Raben[26]	2,000	4·4
Li[27 28]	1,000	7·7
Roos *et al.*[29]	300	3·0
Wilhelmi[30 31]	1,000	3·2
Mills *et al.*[5]	2,000	7·2

Antigenicity of HGH preparations has not proved to be a major problem. Certainly there are instances of high antibody titres arising in patients given growth hormone and consequent arrest of their growth response.[6 7] Raben preparations of HGH have been most widely incriminated for their propensity for causing antibody formation. The violent extraction procedure of this method may damage the hormone molecule, but it has been the most widely used type of HGH preparation. Moreover, as pointed out by Illig,[8] familiarity with the method is followed by the production of batches with minimal antigenicity. She,[8] and Chalkley and Tanner[9] have shown that it is the patient as much as the hormone injected that is responsible for the production of high titres of antibody. The patients who completely lack growth hormone secretion are most liable to form antibodies in response to injected HGH, as if the absence of endogenous hormone made them fail to recognize injected HGH as "self."

Growth Hormone Deficiency in Man

Growth hormone deficiency may be part of panhypopituitarism, the usual cause in the child being a craniopharyngioma, or it may be seen as an isolated pituitary deficiency. It is now clear that the more common cause of growth hormone deficiency is this specific isolated defect, the rest of anterior pituitary function being normal. The syndrome of isolated growth hormone deficiency has been recorded from many centres and the descriptions are surprisingly uniform.[4 10–12]

Affected children are very short for their age but have parents of normal height. Their birth weight is normal, but a subnormal rate of gain in height is detectable very early in infancy. The bone age is also very retarded, but not so severely as the height; consequently their height is short even when compared to their bone age rather than their chronological age. As time passes the height falls below the norm more quickly than the bone maturation. The various parts of the body show the correct proportion to one another, but subcutaneous fat—as shown by skin fold measurements—is thicker than the average normal.[13] The bones of the hand are thin, especially the width of the cortical bone.[12] Muscle bulk is below the normal. At least half the affected males have unusually small penis and poorly formed scrotum. In adult cases puberty has occurred, but somewhat late. The penis remains smaller than normal for the adult, but spermatogenesis is normal.[14] The condition is found at least twice as commonly in boys as in girls; many cases are sporadic, but the defect has been shown in several families, inherited as an autosomal recessive.[4]

Treatment with HGH

The results of the M.R.C. Trial of HGH in the treatment of dwarfism were reported in full by Tanner *et al.*;[4] similar work has been reported in other countries.[12 15 16]

It is important to realize that the normal rate of gain in height is subject to definite seasonal changes, the fastest quarter year of growth being about three times the height velocity of the slowest quarter. Therefore, a full year of uninterrupted therapy is necessary for a valid examination of the influence of HGH on height velocity. Of course, an acceleration of height velocity of such a small and transient nature that statisticians have to pronounce on its significance is of no benefit to the patient. The only valid measure of therapeutic success is an increase in height recognized by the most sceptical relative. Clear benefits of this nature have been recorded only in patients who have growth potential (in terms of unfused epiphyses) and are deficient in growth hormone.

LONG-TERM THERAPY

Long-term HGH therapy has produced the most rewarding gain in height velocity in patients with isolated growth hormone deficiency.

Twenty-eight such patients in the M.R.C. trial achieved a mean height velocity of 9·1 cm for the first full year of treatment, compared with 3·1 cm for the pretreatment year. Those with the lowest height velocities before therapy showed the greatest acceleration when given growth hormone. The bone age velocity was 0·86 before therapy and 1·18 during the year of treatment.

The major point is that the acceleration in height velocity is greater than the acceleration in bone age velocity, thus reversing the situation found in isolated growth hormone deficiency. Tissue changes are also remedied. The administration of HGH reduces the amount of subcutaneous fat,[13] increases bone width, mainly of cortical bone,[12] and increases muscle bulk by cell multiplication rather than by increase in cell size.[17] There is, indeed, the clearest evidence that the defects in growth attributed to lack of growth hormone are corrected by administration of that hormone. A similar response to HGH has been found in children with panhypopituitarism, but all reports indicate that the degree of response is less than that of patients with isolated growth hormone deficiency.

There is no good recorded evidence of HGH therapy being of real benefit to any child with short stature not due to deficiency of growth hormone. Of the 100 patients in the M.R.C. Trial, only those with growth hormone deficiency shown by immunoassay of plasma growth hormone during provocative tests showed a therapeutic response to long-term HGH administration. The short stature of Turner's syndrome is not affected appreciably by growth hormone, nor is the height velocity of the normal small child, or the dwarf of low birth weight. Growth hormone will not accelerate the low height velocity of children undergoing continuous steroid therapy.

INDICATIONS FOR TREATMENT

The evidence to date strongly suggests that growth hormone therapy should be used only in proved cases of growth hormone

deficiency. Within this context the most effective use of growth hormone may be discussed. For research purposes all patients in the M.R.C. trial had a year without treatment after a full year of HGH injections. Those who had shown a therapeutic response to a year's treatment showed a drop in height velocity in the subsequent year to below pretreatment levels; subsequent therapy failed fully to compensate for this. Therefore, once shown to be successful, treatment must be continuous over years. Moreover, being a substitution therapy, HGH injections should be started as early as possible to prevent actual dwarfism.

The very young do not respond any better than older children, but their disability may be prevented rather than alleviated. This is made clear by Figure 1 and 2, which contrast the effects of late and early treatment on height. It must be remembered that the accelerated rate of gain in height gradually diminishes as treatment proceeds. Henneman's report[18] on the rate of height gain achieved in the first six months of therapy gives an unduly optimistic view of continued treatment. The fall-off in height velocity is not due to increasing resistance to the hormone, but conforms to the pattern of catch-up growth as described by Prader *et al.*[19]

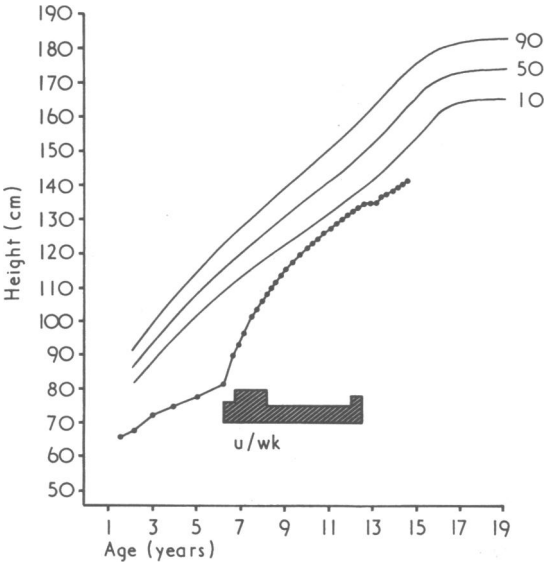

FIG. 1—Late treatment of isolated growth hormone deficiency. Hatched area indicates duration of treatment. Note catch-up type of growth pattern.

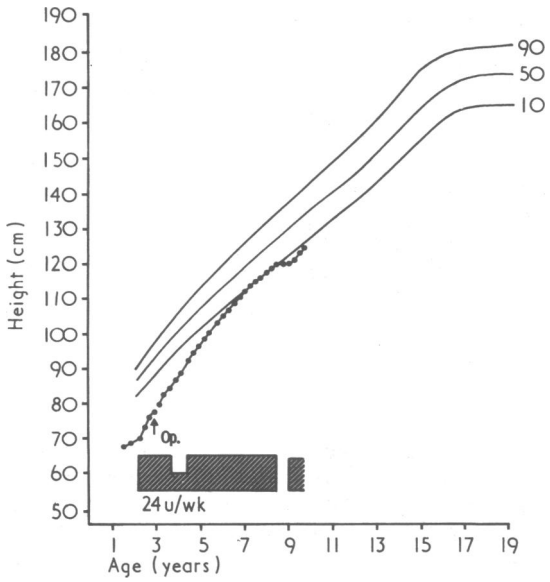

FIG. 2—Early treatment of isolated growth hormone deficiency. Hatched area indicates duration of treatment. Note transient slowing of growth after operation.

DURATION OF TREATMENT

The duration of effective treatment depends on the bone age and not the chronological age of the patient: 20-year-olds have a satisfying response to HGH provided their bone age is grossly retarded. Though data are insufficient for a dogmatic statement, it appears that a bone age of around 14 years heralds the beginning of the end of effective response to HGH.

Growth hormone itself increases the rate of gain in bone age, and every year of therapy brings the bone age at least one year nearer the critical point of no response. Anything that advances bone age more rapidly than height age will seriously diminish the effective duration of HGH therapy. Oestrogens, androgens, and anabolic steroids have such an effect and should never be given to a patient who is likely to require treatment with growth hormone or given during actual treatment with HGH until the patient has approached a height that could not be considered dwarfed in adult life. Of course, the spontaneous onset of puberty indicates that HGH therapy will soon lose its effect as bone age rapidly advances. Patients in whom puberty is delayed must face the fact that they cannot have early sexual maturity and normal height. They and their physicians have to weigh the disability of shortness against that of sexual immaturity.

The time taken for successful HGH treatment, started early to prevent dwarfism, makes heavy demands on the patient and on supplies of human growth hormone; twice-weekly injections have to be given until the child is at least 14 years old if the treatment is to be an effective substitution therapy. World experience suggests that a weekly dose of between 10 and 20 IU HGH gives a very satisfactory response in growth-hormone-deficient children. Doses of up to 40 IU weekly do not appear to produce a significantly better response than 10 IU. On a cost/benefit basis, 10 IU weekly is likely to be the optimum dose.

Role of Growth Hormone in Statural Growth

The hour-to-hour fluctuations of plasma growth hormone levels in response to and control of short-term metabolic adjustments are well-known. Raben[20] suggested that growth hormone was an anticatabolic agent. This certainly fits its role in the short term and might well explain its long-term effect on statural growth, preventing influences that might diminish a genetically determined height velocity.

The effects of growth hormone on stature indicate that its action is dependent on other factors that it cannot over-ride.

It is only an effective stimulus to height velocity when that is low due to growth hormone deficiency. Even under these conditions the effectiveness of growth hormone in maintaining a normal height velocity is dependent on a benign environment. Thyroxine deficiency and even minor excesses of cortisol or its analogues diminish the effectiveness of injected HGH. These effects are distinct from the action of thyroxine and cortisol on the secretion of growth hormone from a normal pituary.

Even non-specific stress, such as a surgical operation, will diminish the height acceleration produced by HGH in a patient deficient in growth hormone. Furthermore, the "catch-up" pattern of growth acceleration due to HGH therapy is to be found in the recovery phase from any growth inhibiting episode. This is certainly true in starvation, when the rate of increase in height is very low and plasma growth hormone levels high. These levels drop during the rapid acceleration of height velocity induced by feeding.[21]

SULPHATION FACTOR

It now appears that growth hormone may well have no direct effect upon skeletal growth, acting only by increasing sulphation factor, which itself stimulates bone growth.[22] Sulphation factor is a peptide produced by the liver and perhaps by the kidney. It incorporates sulphate into growing cartilage cells; hence its name and means of assay. Plasma sulphation factor levels are

high in acromegaly and low in panhypopituitarism or isolated growth hormone deficiency, rising after the injection of HGH. Hall and Uthne[23] have reported that the plasma levels of sulphation factor in growth-hormone-deficient patients receiving continuous HGH therapy are directly proportional to the rate of gain in height.

If plasma sulphation factor concentration does not rise with HGH therapy, no acceleration of height velocity occurs. This point is best illustrated by the type of dwarfism first described by Laron and his associates.[24] The defects of growth are identical to those of isolated growth hormone deficiency, but the plasma level of immunoassayable growth hormone is above normal. Nevertheless, the level of sulphation factor is very low and fails to rise with prolonged HGH therapy, which does not accelerate the rate of gain in height.[25]

Therefore, it appears that growth hormone belies its name. It is one item on a metabolic list of growth-promoting factors that allow an adequate expression of a rate of gain in height that may be genetically determined. It probably has no direct effect on skeletal growth, its target again being the liver. If there is a long-term homoeostatic mechanism linking growth hormone with growth, it is likely to link the plasma level of sulphation factor with the growth-hormone-releasing factor of the hypothalamus.

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Today's Drugs

With the help of expert contributors we print in this section notes on drugs in common use

Respiratory Stimulants

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The story of respiratory stimulants has been repeatedly one of initial enthusiasm followed by gradual disillusionment. This is partly because they have been widely advocated for conditions in which they are not helpful and may be dangerous: neonatal asphyxia,[1] postanaesthetic apnoea, and drug overdosage.[2] And yet an effective respiratory stimulant is needed, particularly for some patients with acute respiratory failure when the alternative may be mechanical ventilation, which, in these patients, carries an appreciable mortality. The indications in patients with chronic respiratory failure are much less clear.

Uses

ACUTE RESPIRATORY FAILURE.

For patients who are hypercapnic, drowsy, and unable to cough adequately a respiratory stimulant is essentially "buying time"—the time necessary to allow other treatment, such as antibiotics, to be fully effective. The greatest need is to keep the patient awake and alert and thus able to cough effectively and remove bronchial secretions.

CHRONIC RESPIRATORY FAILURE.

Though patients may occasionally benefit, the rationale behind giving long-term respiratory stimulants to patients with chronic respiratory failure is very much open to question. A respiratory stimulant will increase both minute ventilation and the work of breathing, which causes an increase in oxygen consumption and carbon dioxide (CO_2) production by the respiratory muscles. Arterial P_{CO_2} depends on the balance between CO_2 production and alveolar ventilation, and as both will be increased by respiratory stimulants there may be little change in arterial P_{CO_2} despite an increase in ventilation.

Contraindications

Respiratory stimulants should not be given to certain patients. Firstly, in conditions where hypoxaemia is not associated with hypercapnia—for example, asthma. If the arterial P_{CO_2} is normal or low then ventilatory drive is adequate and respiratory stimulants will do no good and may be harmful. Secondly, patients with respiratory failure due to neurological or muscular disease; and, finally, great caution should be taken in patients with epilepsy or coronary artery disease.