Therapeutic use of human growth hormone

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A great deal is known about the therapeutic effect of human growth hormone (HGH) on short stature. Raben (1958) reported the acceleration of growth in hypopituitary subjects given HGH 18 years ago. The species specificity of growth hormone means that we must rely on hormone extracted from human pituitaries. It is likely to be a long time before HGH is synthesised and various 'soups' of digested ox pituitary have been of no avail. The only immediate hope for an alternative to HGH is the isolation and synthesis of the growth hormone releasing hormone. If the syndrome of isolated growth hormone deficiency is due to a lack of this hypothalamic hormone rather than an inability of the pituitary itself to secrete growth hormone the logical therapy is obvious.

The amount of 'clinical grade' HGH available from human pituitaries obtained at necropsy will depend largely on the efficiency of the extraction procedures. Raben's (1959) method using acetone-dried pituitaries yielded 4.4 IU per gland. The modification of Wilhelmi's method by Mills *et al.* (1969) obtained about 7.2 IU per gland. Methods using fresh frozen pituitaries vary from that of Roos *et al.* (1963) to the modern development by Lowry (1977) that produced monomer growth hormone at a yield of 16.0 IU per gland. The antigenicity of these products is of importance. The Raben preparation, widely used, promoted antibody formation in a number of patients. The preparations from frozen pituitaries seem less antigenic. The biological potency of each batch of HGH has to be assayed, because it varies considerably, and the potency of the finally ampouled material has to be checked.

Indications for HGH treatment

The indications for using HGH to treat short stature are clear from many well-conducted clinical trials in several countries. The HGH will accelerate growth only in those whose short stature is due to deficient growth hormone secretion. The trouble lies in finding a valid measure of this deficit. The absence

of immunoassayable HGH in a patient's serum is a good indicator of an absence of biologically active HGH. Nevertheless, since normal growth hormone secretion is intermittent it has to be shown that HGH is absent after the pituitary has been stimulated. A serum level of HGH < 7.0 IU/l after appropriate pituitary stimulation indicates definite deficiency, and levels of 7.0 to 14.0 IU/l strongly suggest partial deficiency.

There is still the question of what constitutes an appropriate stimulus to pituitary secretion of growth hormone. As a method of quickly excluding growth hormone deficiency there is nothing better than finding a serum concentration of over 14.0 IU/l, the blood sample being taken from a fasting, frightened child by a clumsy phlebotomist. The whole range of formal testing procedures was reviewed by Frasier (1974). Despite the potential hazards, insulin-induced hypoglycaemia seems to be the most reliable method. Arginine infusion is as cumbersome but less reliable. Penny *et al.* (1969), however, showed that response to different stimuli could vary. Comparing insulin and arginine stimulation in 52 normals, 32 responded to both stimuli but 10 responded only to insulin and 10 only to arginine.

Both these tests are very unphysiological. A more natural approach is to measure HGH levels during 'slow wave' sleep, when 90% of the 24-hour secretion of HGH occurs. Wise *et al.* (1975) reported a case of good response to insulin and arginine but no HGH detectable during sleep. The patient was of short stature and showed a good growth response to injected HGH. Thus the child with clinical evidence of growth hormone deficiency may lack adequate growth hormone secretion despite the fact that abnormal stimuli can elicit HGH secretion. On the other hand, thyroxine deficiency so blunts the capacity of a normal pituitary to secrete growth hormone when stimulated that such tests cannot be interpreted correctly until thyroxine deficiency has been corrected. The curious entity of psychological deprivation has the same effect. Straightforward obesity also diminishes pituitary responsiveness so that a false impression of partial growth hormone deficiency may be given.

Types of growth hormone deficiency

The types of growth hormone deficiency can be classified physiologically. Absence of the hypothalamic growth hormone releasing hormone is presumed in psychological deprivation and is probably the prime cause in many instances of isolated growth hormone deficiency. Direct damage to the anterior pituitary, particularly in children with craniopharyngioma, is an obvious cause of growth hormone deficiency—often, but not always, associated with deficiencies in other anterior pituitary hormones. Finally, the action of growth hormone on target cells may be inhibited by excess cortisol or its synthetic analogues or, since growth is dependent on the release of somatomedin (or, more correctly, somatomedins) by growth hormone, a failure of growth hormone may be due to a deficiency of somatomedins. Thus the Laron dwarf (Laron *et al.*, 1966; Daughaday *et al.*, 1969) has all the clinical characteristics of isolated growth hormone deficiency but has normal serum levels of HGH and does not grow in response to injected HGH. The serum level of somatomedin is very low and does not increase after injections of HGH.

Hall (1971) showed that a single intravenous injection of HGH in a normal subject produced a short-lived rise in serum concentration of HGH but a slow sustained rise in somatomedin concentration, falling gradually over many hours. The direct relation of somatomedin to growth indicates that the frequency of injections of HGH in treatment should be related to the levels of circulating somatomedin rather than to the serum levels of HGH. The recent development of receptor assays, particularly for somatomedin C, is likely to be of practical importance in the future monitoring of therapy.

The clinical picture of growth hormone deficiency is seen most clearly in cases of isolated growth hormone deficiency. Admittedly this monotrophic deficit may later show evidence of gonadotrophin or TSH deficiency. The child deprived of growth hormone will have had a normal birth weight but will be far shorter than expected from parental height. The bone age will be much delayed but the height will be short even for the bone age. There will be relative plumpness, the subcutaneous fat being increased in relation to the thin bones and muscles.

Response to treatment

Such children respond very well to HGH—better than those with such lesions as craniopharyngioma. Subcutaneous fat diminishes immediately and height-gain velocity greatly accelerates to outstrip

by far the rise in bone maturation velocity. This is the opposite of the effects of sex steroids, which increase bone maturation far faster than they increase height. Therapy in cases of growth hormone deficiency is a true replacement treatment and therefore has to be continued over many years until an acceptable adult height is reached. Ideally the diagnosis should be made in infancy, when the slow rate of growth should alert the doctor to the possibility of growth hormone deficiency. Early and continued treatment will prevent dwarfism. The results are much better than those after treatment of established dwarfism. Disappointingly, even now the diagnosis of growth hormone deficiency is often delayed until the child is about 12 years old.

Using quarterly measurements of height, the height-gain velocity induced by HGH in a growth hormone deficient child is maximal in the first three months of therapy and very gradually falls after that. The first year of treatment adds more inches than any subsequent year although the height-gain velocity remains high enough to contribute significantly to statural growth. This fall off in response is in the nature of a catch-up growth curve, as seen, for example, in the treatment of primary hypothyroidism. It has to be distinguished from diminution of response due to some adverse agent.

Failure of the growth hormone deficient child to respond adequately to HGH may rarely be due to antibody formation. The antigenicity of preparations of HGH varies. The Raben preparation has the worst reputation, but the greater use of modified Wilhelmi preparations has shown that they also provoke antibody formation. The Roos preparation from fresh frozen glands seems to be a far less potent antigen. The modern preparations have not been used enough for any conclusion to be drawn. Frasier *et al.* (1974) found antibodies to HGH in 60% of his patients but the mean growth rate was the same for the group with antibodies as for that without them. Illig (1972) considered that antibody formation was more likely to occur in patients who had never had any endogenous growth hormone secretion. However, in terms of the biological response to HGH it is not the presence of antibodies that matters but their capacity to bind HGH that determines interference with growth.

Of the more common factors that diminish the effect of HGH lack of thyroxine and excess of cortisol are very important. Minor excesses of cortisol or its synthetic analogues have a considerable inhibitory effect on HGH. This may explain why a hypopituitary child on replacement therapy usually responds to HGH with only about 65% of the growth seen in treated cases of isolated growth hormone deficiency. It is a real clinical problem to

find a dose of glucocorticoid that keeps the patient safe from the disasters of adrenal failure without severely limiting the growth response to HGH. Any intercurrent illness will diminish growth response. In those with craniopharyngiomas an otherwise inexplicable slowing in induced growth is an alarm that something has gone amiss with the tumour situation. It is an odd fact that in the MRC trial of HGH all 20 males with craniopharyngioma have responded adequately to treatment but 10 of the 30 females have responded inadequately.

Dosage

Clinical hints that a growth hormone deficient child will respond well to HGH are the absence of any other hormonal disturbance, good general health, extreme shortness, and a low bone age. The actual age matters little, but there is a correlation between induced height-gain velocity and low bone age (Preece and Tanner, 1976). The pretreatment height-gain velocity is a poor guide to therapeutic response but there is little to choose between slow and very slow.

Under the best conditions HGH should give a height gain of about 10 cm in the first year. It is difficult to be sure of the right dose because reported regimens of treatment are so different and the comparable potency of the HGH used uncertain. In most countries around 10 IU weekly is given in two or three injections. In the MRC trial 10 or 20 IU has been given weekly in twice-weekly injections. Over 10 years the height gain with the higher dose may be 10 cm more than with the lower dose (Preece *et al.*, 1976). However, it looks as if thrice-weekly injections are somewhat more effective than the twice-weekly regimen and that the most appropriate dose, having regard to the shortage of HGH, is about 10 IU per week. Several authors have reported various regimens of intermittent treatment (Pertzelan *et al.*, 1976), but the height gain seems to be related to the number of months of treatment, as it is with continuous therapy. Claims that intermittent therapy does not have the disadvantage of a fall-off in height-gain velocity as treatment proceeds are not clear from the data presented. It is, of course, an economical way of using HGH.

Finally, there is the problem of sexual maturation. Sex steroids, produced in normal puberty or administered as therapy, always induce a height growth accompanied by a disproportionately rapid advance in bone age, thus cutting down the time left for statural growth. Therefore in patients who do not go into spontaneous puberty there is the choice of more height gain with prolonged HGH therapy or less eventual height but adequate sexual development

caused by sex steroid administration. The normal interaction between growth hormone and sex steroids has been the subject of much debate. Prader and his colleagues (see Zachmann *et al.*, 1976) have shown that HGH is necessary as a permissive factor to allow testosterone to be fully effective as an androgen and as a somatic growth promoter.

Because HGH has been in very short supply (and will probably continue to be) its use in the treatment of short stature has been most fully documented. The indications for its proper use and its effects are now known well enough to provide excellent guidelines for the future.

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