Proper use of growth hormone

Growth hormone treatment is in a state of flux. While it is gratifying that a product which was recently in such short supply should now be available in unlimited quantity thanks to advances in biotechnology, the achievement has been a costly one and the pharmaceutical industry naturally wishes to recoup its investment and make a profit. Only one company in the United Kingdom currently holds a product licence for somatropin (authentic recombinant growth hormone) but competition is expected daily. At a round price of £5000 per patient year there is keen interest by the industry, the profession, and the government as well as the patients and their parents in who should get growth hormone. The equally important questions of who should prescribe, dispense, and pay for growth hormone are interlocked with clinical decision taking but must remain at the fringe of this annotation.

Who needs growth hormone?
The ready availability of somatropin has been followed by an explosion of research into its clinical use. For example somatropin is known to be equipotent with the previously extracted pituitary hormone, free from viral contamination, and daily administration gives a better height velocity than treatment three times a week.1 But the main thrust and excitement in clinical research has come from the discovery of categories of patients who grow faster when given growth hormone but who are not classically growth hormone deficient. Today, it is possible to create three diagnostic categories: (i) growth hormone deficient, where there is unequivocal growth hormone deficit both clinically and biochemically, (ii) growth hormone responsive, where growth hormone has been proved to increase height velocity long term in children who are not classically growth hormone deficient, and (iii) an experimental category where preliminary results of treatment suggest that growth hormone may be beneficial, but confirmation is awaited.

GROWTH HORMONE DEFICIENT PATIENTS
The clearest examples involve damage or destruction of the hypothalamo-pituitary axis as seen in craniopharyngioma, cerebral irradiation, or in developmental anomalies such as septo-optic dysplasia. The diagnoses of ‘isolated growth hormone deficiency’ or ‘panhypopituitarism’ are slightly less satisfying because clearly something is wrong with the axis that is not detectable by current imaging techniques. The vital common denominator is that in all cases of growth hormone deficiency the patient is short, growing slowly, and has an absent or unequivocally subnormal plasma growth hormone response to pharmacological or physiological testing.

GROWTH HORMONE RESPONSIVE PATIENTS
Both the amplitude and frequency of growth hormone pulses increase with age in childhood and at any given age a large child secretes more growth hormone than a small one.2 There emerges the concept of a continuum of growth hormone secretion: between normal growth hormone secretion stimulating normal growth and the unequivocally growth hormone deficient patient there lies a grey zone in which the child secretes some growth hormone but not enough to optimise growth potential. The case of subnormal growth hormone secretion lies at a hypothalamic level or above and may be organic or functional. Studies with growth hormone releasing hormone quickly led to the discovery that up to half the patients identified as ‘isolated growth hormone deficiency’ had hypothalamic rather than pituitary pathology.3 Psychosocial deprivation causes slowing of growth and may mimic growth hormone deficiency, both of which remit on correction of the deprivation.4 The concept of ‘growth hormone insufficiency’ may be easy to grasp,5 but the clinician in consultation still faces a diagnostic dilemma.

When patients with subnormal growth hormone secretion were first characterised a decade ago the term ‘normal variant short stature, NVSS’ was used. Subsequently they have been called ‘constitutional growth delay, CGD’ or ‘short slowly growing children, SSGC’, but no matter what name is used the patient is defined as one who is short, growing slowly, and who responds to growth hormone treatment despite having normal growth hormone biochemistry.6 Clearly the scope for missed diagnosis and misguided clinical practice is immense. The cause of growth abnormality in these patients is commonly looked for in their search for pathology, be it organic or functional, and wary of advocating drug treatment for children who are symptomless and predicted to achieve a socially acceptable adult height. Patients diagnosed as ‘normal variant short stature’ merit a clinical trial of growth hormone treatment but this must be offered in a setting where professional auxology is available to document height velocity off and on growth hormone. If treatment is undertaken an increase of height velocity of more than 2 cm/year over six months is justification for continuing.

Turner’s syndrome is a clearer example of growth hormone responsiveness. There is evidence that growth hormone secretion in Turner’s syndrome may be subnormal in later childhood because of lack of enhancement of pituitary sensitivity to hypothalamic stimulation by ovarian steroids.7 Growth hormone improves linear growth rate in patients with Turner’s syndrome: both chromosomally classic patients and in mosaics, as shown by national trials from six countries. In the large multicentre trial from the United States, 50–70% of patients with Turner’s syndrome who received growth hormone with or without steroids for four years achieved or exceeded their predicted adult height.8 Clinical experience in the United Kingdom,9 confirmed elsewhere, shows that not every patient with this syndrome will respond to growth hormone, but this problem can be overcome with the aid of professional auxology by using each girl as her own therapeutic bioassay. My view is that growth hormone treatment should be discussed with all patients and their families.

EXPERIMENTAL GROWTH HORMONE TREATMENT
The abundance of growth hormone has encouraged...
clinicians to evaluate its potential benefit in other conditions. Growth hormone secretion and treatment was evaluated in two groups of children with intrauterine growth retardation who did not show catch up growth in the first year. In both studies a minority of the subjects had abnormal patterns of physiological growth hormone secretion, but most responded with a clinically important increase in height velocity over one year. Similar results were obtained irrespective of the subjects had stigmata of Silver-Russel syndrome. In the larger study two dose regimens (15 or 30 U/m2/week) were used and the children grew faster on the higher dose. Unfortunately increased height velocity was associated with accelerated bone maturation leading to the conclusion that an improved final height could not be expected from the treatment.

The idea of growth hormone treatment in uraemia is initially surprising because uraemic children have high concentrations of growth hormone in their plasma, but two clinical trials have reported impressive increases in height velocity over six to nine months in response to somatrem (recombinant methionine-growth hormone) or somatropin in conventional doses. This is potentially very important and further detailed information is awaited on the long term response in height, tissue composition, and osseous maturation.

The potential expense of growth hormone treatment should not inhibit clinical scientists from exploring new uses for the hormone, but it lays a heavy burden on them to design good experiments. Those analysing the results of such work must be satisfied that improved growth is achieved in absolute terms and not only in biostatistical units such as standard deviation scores. Clinical practice should advance cautiously; only in adulthood will the full consequences of paediatric treatment be appreciated.

**Dose?**

The dose of growth hormone used in the United Kingdom has arisen from historical practice; most patients are on 12 or 14 U/week given as 2 U subcutaneous daily injections, or less commonly as three injections of 4 U/week. This results in a wide range of dosage in terms of body weight or surface area and some paediatricians have been pragmatic and halved the dose for patients under 20 kg. Improvements in the packaging of growth hormone now mean that this rough and ready approach is no longer appropriate. The doctor needs to calculate what dose will optimise therapeutic effect at minimum cost. This is likely to be calculated on a body weight basis and given daily.

A review of growth hormone dose response showed clearly that growth rate is directly proportional to the logarithmic dose given; in other words a physiological effect merges into a pharmacological one. While it is easy to agree that physiological growth hormone replacement is desirable, the profession is divided on the use of growth hormone as a pharmacological tool. Some investigators take the view that if a given dose does not produce the effect they are seeking in a novel group of patients such as those described as 'normal variant short stature' then more will be better. They monitor their clinical trials empirically by looking for side effects such as glucose intolerance, but I find this approach conceptually unsatisfactory. If growth hormone works in physiological replacement dosage there is a priori evidence that the body lacked growth hormone; if pharmacological dosage is required to produce an effect there is no endogenous growth hormone lack and growth hormone treatment is not indicated.

**Comment**

This annotation has focused on the use of growth hormone to stimulate growth in children and other therapeutic possibilities that may have considerable impact on paediatric practice, such as growth hormone induction of anabolic postoperatively, have of necessity been excluded.

Cost/benefit considerations come into every consultation where growth hormone treatment is discussed with a family. Happily, good rapport has developed in the United Kingdom between family practitioners and hospital based paediatric endocrinologists whereby the former prescribe and oversee the administration of this costly product and the latter provide a diagnostic and monitoring service that is essential for the correct use of the hormone.

The potential risks associated with growth hormone treatment must always be discussed before treatment is recommended. Physicians can now give unequivocal reassurance that there is no risk of Creutzfeldt-Jakob disease when hormone made by recombinant biotechnology is used. The question of leukaemia is more complex and a recent comprehensive review concludes: Though no clear evidence of a strikingly augmented leukaemia incidence is found world-wide, the available data call for increased attention. Other risks such as diabetes are negligible so long as growth hormone is used in physiological replacement dosage. This can be defined as the amount required for normal growth in a growth hormone deficient subject. Growth hormone induced gigantism illustrates dramatically how the hormone can stimulate growth pathologically and I would not consider it good clinical practice to use high dose growth hormone regimens in refractory patients whatever their primary diagnosis.

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