Who should get growth hormone?

The potential availability of growth hormone for the treatment of short stature is likely to increase dramatically in the near future as a result of genetic engineering. Advances in the manufacture of methionyl growth hormone, synthesised by bacteria, have resulted in a product of acceptable purity and freedom from antigenic contamination. Interim reports of clinical trials using methionyl growth hormone show it to be at least as good as pituitary growth hormone in stimulating the growth of hormone-deficient children. This is good news since there has always been a worldwide shortage of pituitary growth hormone, and in the United Kingdom, where adequate amounts have been available for the treatment of deficient children since 1964, there are chronic problems in maintaining a supply of pituitary glands to meet clinical demand. If methionyl growth hormone becomes freely available these difficulties will be resolved, but we may then be faced with others which will certainly include a critical evaluation of the indications for treatment.

The pharmaceutical industry hopes that the clinical market will not be limited to the treatment of growth hormone-deficient children, and there is speculation, based on little or no evidence, that growth hormone will also accelerate the healing of fractures, wounds, and burns. Concentrating on growth hormone as a stimulant of skeletal growth we face the prospect that it may be used not only to replace a physiological lack but also as a pharmacological tool to increase the final height of short children. Between these extremes lies a complicated diagnostic spectrum which can best be appreciated by a précis of the aetiology and clinical evaluation of growth hormone problems encountered in childhood.

Aetiology

Abnormal growth hormone release associated with undergrowth may be considered rationally in the sequence: higher brain centres, hypothalamus, hypophysis, the growth hormone molecule, the growth hormone receptor, and postreceptor events. It is not always easy to distinguish intrinsic abnormalities of hypothalamic function from those originating in higher centres but the growth failure mimicking growth hormone deficiency that results from psychosocial deprivation is the most important example, because it is relatively common and because it illustrates the pitfalls facing a paediatrician eager to make a diagnosis which can then be treated by years of growth hormone treatment administered thrice weekly by injection. Our imperfect understanding of the relation between the higher brain centres and the hypothalamus is only slightly greater than that of the hypothalamo-hypophysial axis. Growth hormone deficiency due to anatomic destruction of the hypophysis, for example by craniopharyngioma, is the easiest to understand. It is not difficult to extrapolate to other structural lesions of the axis: abnormal development (septo-optic dysplasia); infiltrates (histiocytosis x); or tumours (glioma, germinoma, and astrocytoma). The radioresistance of the hypophysis has resulted in a false sense of security among those caring for children undergoing cranial radiotherapy, either curative in the treatment of a tumour (for example medulloblastoma) or prophylactic (for example in the management of leukaemia). The hypothalamus is more radiosensitive than the hypophysis and there is now increasing recognition of abnormal hypothalamo-hypophysial function in the long term survivors of cranial radiotherapy. Some have presented as growth hormone deficient;1 in others, body proportions are abnormal suggesting disturbance of gonadotrophin and sex steroid secretion at the time of puberty.2 Another poorly understood aspect of the hypothalamo-hypophysial axis is the effect of sex steroids on growth hormone secretion. Total or partial deficiency has been diagnosed prepubertally in a number of patients who have subsequently been shown to have normal growth hormone secretion as adults.3 It is partly for this reason that sex steroid priming is a prerequisite for the biochemical investigation of deficiency in children with bone ages of more than 10 years.4 With the appreciation that hypothalamo-hypophysial interaction is both more complicated and subtle than has been generally understood, clinicians are becoming receptive to evidence of hypothalamic malfunction when assessing a case of potential growth hormone deficiency. The prime example is a child who fulfils all the auxological criteria of deficiency but who has 'normal' peak plasma growth hormone concentrations on biochemical testing. It has been argued that such a patient, while responding to pharmacological stimulation of the hypophysis, is unable to secrete adequate growth hormone physiologically to sustain normal growth. Such thinking has fuelled a debate about what are physiological (for example exercise, sleep) and what are pharma-
ological (for example clonidine, L-dopa) stimuli of growth hormone secretion. This is, in my view, peripheral to the main issue since all tests for growth hormone secretion so far evaluated have an appreciable false positive and false negative failure rate, partly because of innate biological variation but more importantly due to the chronic imprecision which is inherent in growth hormone immunoassay.

Within the hypophysis there may be a block in growth hormone biosynthesis or a molecule may be secreted that is immunoreactive but not biologically effective. The latter example is also compatible with the patient who seems to be deficient clinically but has a ‘normal’ response to biochemical testing. Finally there are the rare examples of short stature due to growth hormone receptor and postreceptor disorders.

Clinical evaluation

It is against this aetiological background that the patient with short stature who is a potential candidate for growth hormone treatment is assessed. In the initial clinical evaluation other pathology that might result in failure to grow must be excluded, of which the most difficult may be the evaluation of psychosocial problems. Then comes the assessment of growth potential taking a careful account of the rates of height gain and osseous maturation, and the matching of adult height so predicted with that expected from the parental heights. Most short children seen in a growth clinic are organically normal and the paediatrician provides a valuable service if the family can be authoritatively reassured that this is so. By careful measurement of the patient, the parents, and the bone age, sound diagnostic advice can often be given without recourse to a single venepuncture.

In contrast are the children who are growing slowly, who may be shorter than their peers, and who usually have a retarded bone age. Auxological analysis will show that they are unlikely to fulfil their genetic potential. If biochemical tests confirm growth hormone deficiency, all well and good: treatment is available. The dilemma arises when formal tests of growth hormone release show ‘normal’ results—that is a peak plasma growth hormone concentration of more than 15 mU/l. In these children expert assessment of all aspects of hypothalamic-hypophysial structure and function should follow. This will include measurement of the response of hypothypophysal hormones (in particular thyroid stimulating hormone, prolactin, follicle stimulating hormone and luteinising hormone) to stimulation by releasing hormones and may include sophisticated neuroradiological investigations.

Who should be treated?

The rules governing growth hormone treatment vary around the world; some countries have a national policy, in others the decision is left to the individual paediatrician. This has lead to some interesting studies. Grunt and Enriquez were the first to report that children with idiopathic short stature and normal growth hormone secretion grew faster when treated with growth hormone and this observation has been confirmed in a large national series. Injections of growth hormone may cause an acute rise in somatomedin concentrations and stimulate growth in some short children. This could be due to the secretion of a growth hormone molecule that is immunoreactive but not bioactive—a view supported by the finding of a discrepancy between immunoassay and homologous radioreceptor bioassay results. As interest in this aspect of treatment has waxed there have been publications reporting that growth hormone increases height velocity in ‘normal-variant short stature’ and in ‘short normal children’ which have heightened the interest of doctors and patients alike in the subject of growth. But the evidence must be reviewed critically—what is ‘normal’? A peak plasma growth hormone concentration above a certain defined point is no longer reassurance of normality. High resolution computed tomography has shown structural abnormality in the pituitary of nine of 12 subjects with short stature, slow growth rate, but normal endocrinology and in two of four patients presenting with anorexia. Another defect in the clinical studies of ‘normal’ children has been the lack of an appropriate control: treatment with placebo, an omission that would not have occurred had the species studied not been man.

If we accept there are children whom some will call ‘normal’ but who respond to physiological growth hormone replacement treatment we must also appreciate that some doctors will contemplate using the hormone in pharmacological doses to stimulate the growth of the unequivocally normal child. Excess endogenous secretion before puberty may present as gigantism and chronic growth hormone administration to normal animals results in skeletal overgrowth. But there are also side effects such as the development of diabetes mellitus and the small but real risk of developing growth hormone antibodies that block all further growth. Few if any paediatricians would use growth hormone as a pharmacological tool to increase the height of a normal child but it is possible that there may be a use for the hormone in this way to improve the lot of children dwarfed by skeletal dysplasia. Preliminary reports that growth hormone treatment increases
the height velocity in Turner’s syndrome warrant further study since short stature is the most socially handicapping problem these girls face.

The importance of short, slowly growing children with normal peak plasma growth hormone concentrations and girls with Turner’s syndrome as further possible categories meriting growth hormone treatment, in addition to those children with unequivocal deficiency who are already accepted for treatment, has lead the Health Services Human Growth Hormone Committee to initiate a multicentre clinical trial in the United Kingdom to study this problem. In the trial each participant will be used as his or her own control. Height and osseous maturation will be measured at a recognised growth clinic before treatment, for two six month periods of treatment with growth hormone and placebo, and for six months after one year’s treatment has been completed. In this way it is hoped to provide in 1986 a clearer answer to the question ‘who should get growth hormone?’

References

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The role of exercise tests in determining growth hormone deficiency is discussed by Nicoll et al and de San Lazaro et al in pages 1177–1182 of this issue.