Growth hormone for adults

Nearly 40 years ago it was shown that human pituitary growth hormone (but not bovine or ovine hormone) was a potent protein anabolic agent in normal adults, with a useful fat-mobilizing action in addition[1]. But, because of the considerable difficulty in obtaining the human hormone, research and clinical use was entirely concentrated on its major effect, growth promotion in growth-hormone-deficient children. In 1987 the first biosynthetic human growth hormone was reported equally effective in children, and the therapeutic indications were gradually widened in children of short stature.

There is often a seminal observation which initiates a new aspect of clinical investigation, and one such was Preece's report on cross-sectional scans of the thigh of a hypopituitary patient who had been treated for 10 years with human growth hormone and had then stopped the daily injections for 1 year at age 18; the loss of muscle bulk and increase of subcutaneous fat was very striking[2] (Figure 1). Soon after this we began to see the results of careful randomized clinical trials of recombinant human growth treatment of growth-hormone-deficient adults[3–6], all confirming the initial visual impression.

The clinical pattern of growth hormone deficiency in adults is now becoming clear[7,8]. It includes subnormal psychological wellbeing, low vitality and social isolation, although these may be difficult to identify without complete questionnaires. The physical signs include increased body fat and waist–hip ratio, and reduction in lean body mass and muscle bulk with low muscle strength and exercise performance. Laboratory features include subnormal extracellular fluid volume, bone mineral density, glomerular filtration rate, basal metabolic rate and plasma high-density lipoprotein cholesterol. These findings are in accord with previous experimental and clinical studies indicating that growth hormone was necessary for regulation of muscle, bone and lipid metabolism in adults and suggesting that its deficiency would result in identifiable troubles. Recombinant human pituitary growth hormone is now licensed in the UK for replacement treatment in growth-hormone-deficient adults as well as children[9,10].

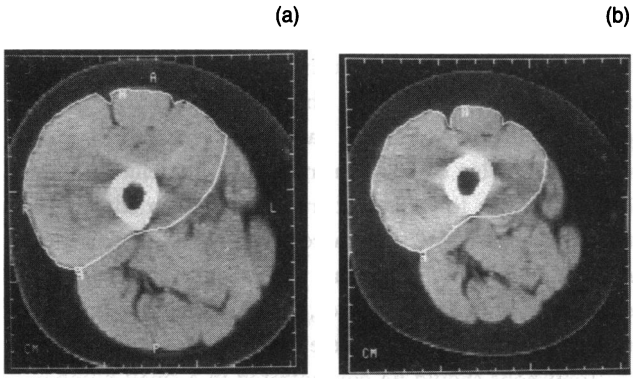

Figure 1 **Cross-sectional CT scan of the thigh of a panhypopituitary patient aged 18, who had received regular growth hormone replacement therapy for 10 years: (a) 3 months before stopping therapy, (b) 12 months after stopping therapy.** Reproduced, by permission, from *Acta Paediatr* 1987;**331**:77 (suppl)

One of the outcomes of the careful prospective analysis of hypopituitary children treated with human growth hormone, and of longer-term epidemiological studies in adults with hypopituitarism, is the recognition that these conditions carry a definite premature mortality, largely from vascular disorders, independent of the actual cause of the pituitary deficiency or its duration[11]. Routine replacement therapy with cortisol, thyroxine and sex hormones does not eliminate this effect, and it is possible that growth hormone deficiency is a factor. Further analysis of large series of patients treated for hypopituitarism over many years is needed. There are other possible indications, beyond the hypopituitary state, for a potent fat-mobilizing protein-anabolic therapeutic substance. Growth hormone secretion falls spontaneously in old age and long-term supplementation might be beneficial in several ways. The fat mobilization effect could have implications for management of obesity. There is probably a useful effect in prevention of osteoporosis, but how this would interact with all the other metabolic and endocrine aspects of that condition is uncertain. There is a positive effect on cardiac function, but whether that has any therapeutic relevance, except in prevention of the deficiency state, is unknown. Early studies of growth hormone supplementation for prevention of post-surgical catabolism[12] or acceleration of recovery from protein malnutrition[13] were limited by inadequate supplies of the hormone. The recombinant product removes that difficulty, but it remains very expensive and cost/benefit analysis will be important[9,10].

High cost is not the only reason for doubt about long-term growth hormone replacement in hypopituitary adults. The vision of continued daily injections for the rest of life will deter most adolescents who have got to the top of a successful growth curve, often with considerable parental encouragement. The new pen injectors are certainly easy to use; whether an intermittent (weekly) injection would have long-term value for the adult has not been assessed. Undoubtedly daily injections would be more physiological, but a weekly boost might be better than nothing at all. There is a useful rapid effect on serum insulin-like growth factor 1 levels, which will probably become accepted as a biochemical marker of growth hormone action and facilitate studies of therapeutic compliance. The possible misuse of recombinant human growth hormone in sport remains a concern; in acromegaly the effects of persistent excess endogenous

growth hormone include hypertension, osteoarthritis, diabetes and large bowel cancer. The order of magnitude of difference between the relatively normal level of serum growth hormone achieved intermittently on replacement injection therapy, and the persistent inappropriately high levels found in active acromegaly suggests that these potential therapeutic problems will not be seen in clinical practice.

The action of the circulating growth hormone molecule is to dimerize the extracellular domain of the transmembrane growth hormone receptor: this action sets in train the intracellular effects which eventually produce the therapeutic result. Circulating fragments of the receptor also function as a physiological binding protein[14,15]. The pharmacological challenge is to produce an orally active 'designer drug' that will likewise dimerize the receptor. When and if that is identified, the clinical role for this protein anabolic and lipolytic substance will be greatly enhanced.

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