Optimum Use of Growth Hormone in Children

Z. Laron and O. Butenandt
Institute of Pediatric and Adolescent Endocrinology, Beilinson Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, and Kinderklinik, Universität Munich, Munich, Federal Republic of Germany

Since its first therapeutic use in hypopituitarism (Raben 1958), human growth hormone (hGH) has been used increasingly, the only restriction being the availability of the hormone. Until 1985 only hGH extracted from the pituitary was available, and the only indication for its use was in GH-deficient children whose long bone epiphyses had not yet closed. Since the early 1980s recombinant biosynthetic hGH has been available (Olson et al. 1981) and its almost unlimited supply has led to investigation of other indications. At first only methionyl-hGH was available (Kaplan et al. 1986), but due to its immunogenicity authentic recombinant hGH was soon prepared (Fryklund 1987).

Uncontestably the optimal use of hGH is as a replacement agent in growth hormone deficiency (GHD), whether isolated (IGHD) or in combination with other pituitary hormones (MPHD).

1. Growth Hormone Deficiency in Childhood

Since the first description by Raben (1958) of the effectiveness of a human pituitary extract preparation in accelerating the growth of a patient with hypopituitarism, many thousands of patients all over the world have been treated with hGH (Raitt 1987a). Many pharmacological and physiological tests have been devised to diagnose GHD (Laron & Butenandt 1983) and many papers have been written on the efficacy of its treatment (Laron et al. 1987a). The main conclusions are as follows:

1. The diagnosis of GHD should be made as early as possible since initiation of replacement therapy at an early age results in faster and greater ‘catch up growth’ and normalisation of height (Laron et al. 1987b; Vanderschueren-Lodeweyckx et al. 1987).
2. Daily injections, especially at night (mimicking the physiological highest pulse), are more effective than a regimen of injections 3 times weekly (Guyda & Dean 1987; Smith et al. 1988).
3. The total effective dose of the hormone ranges between 0.3 and 0.6 U/kg/week in 6 or 7 divided doses. Smaller children react to the smaller doses (Frasier 1987).
4. Studies of the effect of 5 years’ treatment with hGH on sitting height and subischial leg length (Bundak et al. 1988) have found that growth rates of both body segments are affected equally.

Growth before puberty is a major determinant of final height, as reflected by a strong correlation between final height and height at onset of puberty (Bourguignon 1988). In view of the fact that during normal puberty there is an augmentation of the 24-hour hGH pulsations (Mauras et al. 1987), the question arose as to whether hGH replacement doses needed augmentation during puberty. A thrice-weekly dose is definitely insufficient as it may permit premature closure of the bony epiphyses in IGHD patients and thus reduce the expected height (Van der Werff ten Bosch & Bot 1990). The daily optimal effective hormone dose to be administered in puberty has not yet been established (Bourguig-
non & Van Vliet 1989). However, when the efficacy of the recombinant hGH preparations (rhGH) and the pituitary-extracted hormone were compared in patients with hGH deficiency, no differences were found (Holcombe et al. 1990; Pertzelan & Laron, unpublished data). Whether postponement of puberty in IGHD patients by GnRH analogues is beneficial to the final height of the patients is another controversial issue (Bourguignon & Van Vliet 1989; Dacou-Voutetakis & Kontsiotou-Marinaki 1988; Toublanc 1989).

If diagnosed and treated early and in a regular fashion with progressive dose adjustments, children with hGH deficiency reach normal height (Bourguignon & Van Vliet 1989; Laron et al. 1987b). However, to ensure compliance in children and social adjustment in adult hypopituitary patients, continuous psychosocial counselling has been found to be very beneficial (Galatzer et al. 1987) in comparison to groups where counselling has not been given (Bjork et al. 1989; Blizzard et al. 1986; Dean et al. 1985).

2. Adult GH-Deficient Patients

The recent free availability for hGH has raised the question of whether hGH therapy should not be continued after bone epiphyseal closure, and resumed in GHD adults who have received treatment in childhood. A small number of studies, in relatively few patients (Jorgensen et al. 1989; Solomon et al. 1989; Whitehead et al. 1989), revealed that between 4 and 6 months' treatment with hGH in doses of 0.06 to 0.07 U/kg/day resulted in an increase in lean body mass and decrease in body fat mass and fasting plasma cholesterol levels. There was no change in bodyweight or muscle fibre diameter (Whitehead et al. 1989), but there was a significant rise in exercise capacity (Jorgensen et al. 1989). The heart rate both at rest and after maximum exercise increased significantly during hGH therapy, as did the glomerular filtration rate.

It has been suggested that the physiological decline in hGH secretion with advancing age (Gil-Ad et al. 1984; Ho et al. 1987) contributes to the catabolic processes involved in aging. Rudman et al. (1990) therefore performed a trial in 12 men aged between 69 and 93 years, treating them with subcutaneous hGH 0.06 U/kg 3 times a week. The administration of hGH for 6 months was accompanied by a 9% increase in lean body mass, 14% decrease in adipose tissue, and a slight increase in average vertebral bone density. Even 4 days of pulsatile physiological replacement in hGH in 3 adult GHD patients increased glucose and glycerol production and raised insulin levels (Vance & Kinter 1990).

Undoubtedly, further studies are necessary in adults with GHD or physiological reduced secretion in old age to establish whether hGH is indicated in these states.

3. GH Therapy in Non-GHD Children (Nonconventional hGH Therapy)

Short stature, defined by height more than 2 SD below the mean, is a social stigma in the affluent society (Stabler & Underwood 1986), which seeks more in every possible parameter. Short children are often the underdogs in school and additionally it is frequently believed that success in life is often linked to tall stature.

The availability of unlimited amounts of hGH, and the finding that short stature is often associated with low 24-hour GH secretion, or irregular secretion (neurosecretory dysfunction) [Albertsson-Wikland & Rosberg 1988] has led to the initiation of many trials to improve the growth velocity of children with so-called 'constitutional short stature'.

Data on 4 subjects diagnosed as 'small/delay' in the study of Tanner et al. (1971) were not conclusive. The UK Human Growth Hormone Committee's trial, which was terminated in 1985 due to the withdrawal of pituitary hGH in that country, involved 11 children (Buchanan et al. 1987). The results of the 6-month trial with an hGH dose of 4IU 3 times weekly were difficult to interpret. In another study (Albertsson-Wikland & Rosberg 1988), all children had normal responses to pharmacological stimuli, although almost all had low or im-