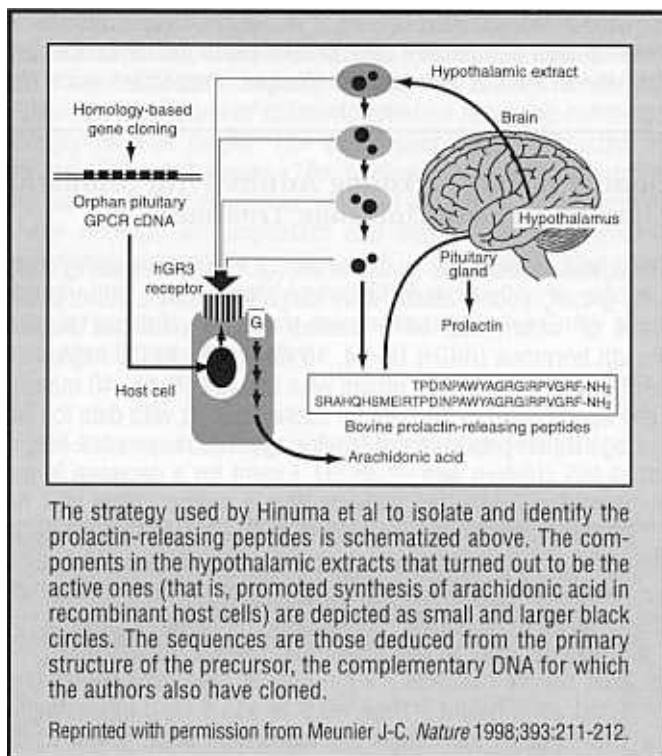


long been sought and now appears to have been isolated. The physiologic role of the prolactin-releasing peptides is unclear, and their diagnostic or therapeutic relevance remains to be assessed. The "reverse" process by which the prolactin-releasing peptides were found (ie, identification of an orphan receptor and then its ligands) indicates the revolution in biologic investigation in which we have the privilege of participating. Details concerning the lactotroph cell membrane receptor specific for the prolactin-releasing peptides are awaited. Meunier's comments and entire article (*Nature* 1998;393:211-212) are exceedingly worthwhile reading.

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GH Dependence and GH Withdrawal Syndrome in GH Treatment of Short Normal Children: Evidence From Growth and Cardiac Output

Lampit et al evaluated the efficacy of interrupted growth hormone (GH) therapy in prepubertal children with idiopathic short stature (ISS). Their protocol was to treat normal short children for a period of 3 years or until they reached the 25th percentile and then to discontinue therapy at a young age (no more than 9 years of age) and follow them until final height. The criteria for ISS were height <-2 SD, growth rate more than -1 SDS, bone age $<75\%$ of chronologic age, and serum GH concentration following arginine stimulation of >10 $\mu\text{g/L}$. Thirty-four children were studied, 12 of whom served as a control group. In addition to measuring the children, Doppler echocardiographic evaluation was performed before recombinant human GH (rhGH) therapy, yearly for 2 years during therapy, and at 6 and 12 months after the cessation of therapy.

The children receiving rhGH were treated until their height reached the 25th percentile but for no longer than 3 years, even if they had not reached this percentile. Nineteen of the children completed 3 years of rhGH therapy (0.9 mg/m^2 daily). During the first year of treatment, the growth velocity accelerated as expected. After withdrawal of rhGH, growth decelerated in every child over a 6-month period to a velocity that was significantly lower than pretreatment values. The growth velocity recovered to pretreatment values by the fourth semiannual measurement. Height SDS also increased in the treatment group and then declined somewhat in the second year of therapy. The GH response to arginine was not significantly different after rhGH therapy. Insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) remained unchanged throughout the

study. However, systolic and diastolic parameters fell significantly during the initial 6 months of rhGH withdrawal and remained low for 12 months. Aortic cardiac output also fell significantly during the initial 6 months of rhGH withdrawal. No child had any symptoms referable to these cardiac changes.

The authors state that these data suggest that it may be feasible to interrupt rhGH prior to puberty in order to achieve an improved final height, but they will not know this for certain until the patients reach their final height. More interestingly, their report suggests that rhGH treatment is associated with the development of a physical adaptation to continuous high levels of GH. The rhGH withdrawal symptoms were not induced by alterations of serum GH or IGF-1.

Lampit M, et al. *Eur J Endocrinol* 1998;138:401-407.

Editor's comment: This is a fascinating report. It has become more and more apparent that adults with GH deficiency (GHD) have significant improvement in cardiac function when they are restarted and maintained on replacement therapy. It would appear that the administration of rhGH to children who do not manifest GHD induces a dependency on rhGH for cardiac function.

Indeed, when rhGH is interrupted there is a significant reduction in cardiac output. Although the authors state that there have been no clinical symptoms associated with the cardiac findings, the effect of either longer periods of rhGH administration or longer

withdrawal has not been studied. It would be of interest to repeat these studies periodically over several years before concluding that there are no permanent changes associated with the

initiation and subsequent withdrawal of rhGH in normal short children.

William L. Clarke, MD

Quality of Life of Young Adults With Idiopathic Short Stature: Effect of Growth Hormone Treatment

The authors assess the quality of life (QOL) and well-being of 89 fully grown, young adults with idiopathic short stature (ISS), some of whom had been treated with recombinant human growth hormone (rhGH) (N=24, 16 males; 0.2 to 0.3 mg/kg/wk for 3.8 to 8.1 years) and others who had not (N=65, 40 males). They also compared the data for these subjects with data for the average Dutch population of similar age. The mean adult height for all ISS children was -2.35 SD. Except for a decrease in the number of rhGH-treated subjects with a partner, there was no difference between the rhGH-treated and nontreated subjects with ISS in educational attainment, state of general health, personality inventory, or psychosocial/employment difficulties encountered because of short stature. The adult heights of the 2 populations were similar. The rhGH-treated subjects achieved an adult stature that was 3.3 cm greater than the pretreatment predicted adult height (range, -9.9 to +13.4 cm); interestingly, the rhGH-treated individuals estimated their adult height to be 13 cm (range, 0 to 28 cm) greater than they would have reached without rhGH administration, a perception also shared by their parents. Although expressing a desire to be taller, when the rhGH-treated and nontreated ISS subjects were asked if they were willing to risk loss of longevity in order to achieve greater stature by taking a lifelong medication, or to risk loss of life by a height-increasing surgical procedure, only a minority (11% to 22%) indicated a willingness to do so. Most ISS subjects were satisfied with their heights. In comparison to the general

Dutch population, there were no meaningful differences in QOL of the ISS subjects, whether treated with rhGH or not (see Table). The significance of the lower frequency of a partner in the rhGH-treated ISS subjects was unclear but not considered significant as it did not differ from the general Dutch population. The authors concluded that "the QOL of rhGH-treated and untreated young adults with ISS was similar and equal to the general population."

Rekers-Momberg LTM, et al. *Acta Paediatr* 1998;87:865-870.

Editor's comment: These data indicate that: (1) subjects with ISS do not differ from taller peers in their QOL; (2) administration of rhGH does not meaningfully increase adult stature or improve the QOL of treated subjects; and (3) the perception of the effectiveness of rhGH in increasing height is vastly overestimated by the treated subjects and their families. In the experience of this physician, it is the concern of the parents rather than of the child who has been brought with ISS for pediatric endocrine consultation. It is essential that the pediatric endocrinologist confronted with the normal child with ISS fully inform the family about the limited expectations of therapy with rhGH on adult stature and future well-being, and emphasize the greater likelihood that the child's stature will have minimal impact on his function as an adult.

Allen W. Root, MD

The Mean (SD) Values for Dimensions of the Dutch Restricted Version of the Minnesota Multiphasic Personality Inventory (NVM) for rhGH-Treated and Control Children With Idiopathic Short Stature (ISS)

Dimension of the NVM	Treated ISS (n = 17)	Controls ISS (n = 47)	Standard Population (n = 809)
Negativism	17.9 (10.3)	15.7 (9.7)	14.7 (7.7)
Somatization	5.9 (6.6)	4.7 (4.4)	5.3 (5.3)
Shyness	8.6 (7.5)	9.6 (7.6)	8.0 (6.4)
Severe psychopathology	3.1 (2.4)	2.7 (3.5)	2.7 (2.7)
Extroversion	20.4 (5.1)	19.7 (4.8)	17.1 (5.3)

Reprinted with permission from Rekers-Momberg LTM, et al. *Acta Paediatr* 1998;87:865-870.

Final Height After Combined Growth Hormone and Gonadotropin-Releasing Hormone Analogue Therapy in Short Healthy Children Entering Into Normally Timed Puberty

Controversy continues as to the feasibility of using gonadotropin-releasing hormone analogues (GnRHa) in combination with recombinant human growth hormone (rhGH)

to increase final height by delaying puberty and slowing bone maturation in short non-growth hormone-deficient (GHD) children. Lanes and Gunczler evaluated the effect of 2 1/2 years of