

Editor's Comment: The authors recall several studies in which catch-up growth in pre-term infants has been stated to occur up until adolescence, and note that the patients in this study should be followed at least through school age. The data are intriguing however, for several other reasons. First, it is possible that these very young children (less than 30 weeks gestation) may respond with accelerated growth to recombinant growth hormone therapy in much the same way as do children with intrauterine growth retardation. Initiation of such therapy at a young age might significantly improve not only final

height, but developmental milestones as well. The discrepancy in head circumference in the very pre-term infant, although minimal, is nonetheless of considerable concern. Thus as the authors point out, it would be important to carefully record growth patterns, and developmental milestones over time in the attempt to define those children who might benefit most from earlier hormonal investigation and intervention. It would appear that the Swiss Minimal Neonatal Data Set is an excellent resource for the collection and analysis on such data.

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Adult Height in Advanced Puberty with or without Gonadotropin Hormone Releasing Hormone Analog Treatment

The authors define "advanced puberty" as "the onset of puberty in girls between 8 and 10 years and in boys between 9 and 11 years." (Others might also use the term "early puberty" for such subjects.) In a retrospective assessment of the effect of a gonadotropin releasing hormone agonist (GnRHa - D-Trp⁶-GnRH) upon adult stature in children with "advanced puberty," the authors administered GnRHa for 2-2.4 years to 9 adolescent girls with serum estradiol concentrations in excess of 20 pg/mL, and 8 pubertal boys with testosterone values greater than 100 ng/dL who had a pubertal gonadotropin secretory response to GnRH. Mean adult height of treated subjects was compared to that of a control group of untreated subjects. In treated girls, mean adult stature (155.3 cm) was insignificantly different from pretreatment predicted height (151.9 cm). In control females (N=31), mean adult and predicted heights were also similar (157 cm and 156.7 cm, respectively). In both groups, adult heights were close to their target heights. In treated boys, mean adult height (164.1 cm) was less than mean predicted height (173.2 cm) and mean target height (170.4 cm). In untreated boys (N=9), adult height, predicted, and target heights were similar (169.1, 170.8, and 170.2 cm, respectively). The authors concluded: "These data suggest that advanced puberty decreases the growth potential by about 5 cm, and that GnRHa treatment does not prevent this."

Couto-Silva AC, et al. *J Pediatr Endocrinol Metab* 2002;15:297-305.

Editor's Comment: Luckily, GnRHa did not increase adult stature in girls with "advanced puberty" and may even have led to decreased stature in boys. While under specific and individual circumstances (such as major behavioral problems, disabling physical handicaps, or significant developmental delay), one might consider interruption of pubertal development in subjects of normal adolescent age, to do so for the purpose of achieving a greater adult stature is an unjustified use of agents such as GnRHa. Similarly, the use of recombinant human growth hormone (rhGH) to increase to a minimal extent adult stature in normal but short children is unjustified medically, psychosocially, or financially.¹ Unfortunately, we may shortly expect to read a manuscript in which both GnRHa and rhGH have been administered to children with "advanced puberty."^{2,3} At what point did the pediatric endocrinologist cease being a physician-scientist and become a physician-cosmetologist?

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References

1. Finkelstein BS, et al. *Arch Pediatr Adolesc Med* 2002;156:230-240.
2. Kamp GA, et al. *J Clin Endocrinol Metab* 2001;86:2969-2975.
3. Kaplowitz PB. *J Clin Endocrinol Metab* 2001;86:2965-2968.

GH Anabolic Effects of GC-Dependent Children with IBD

This pilot study utilizing 6 boys and 4 girls was designed to determine whether rhGH could overcome some of the catabolic effects of chronic glucocorticoid (CG) treatment (24 months) of IBD. Subcutaneous rhGH (0.05 mg/kg/d) was given for a minimum of 6 months. Seven patients continued for 12 months. Body composition

changed favorably with increased fat free mass and decreased fat mass. Linear growth velocity increased from 3.5 ± 0.4 cm/yr pre-rhGH to 7.7 ± 0.9 cm/yr after 6 months. The GV persisted for the next 6 months in all 7 treated. Bone calcium accretion increased as did alkaline phosphate specific for bone [(a measure of bone

formation) $p = .03$]. Fasting and 2 hour post prandial glucose levels, fasting insulin levels, and HbA1C remained in the normal range. The authors concluded that treatment with rhGH at the doses used has beneficial effects in prednisone-dependent growing children, on body composition without detrimental effects in carbohydrate metabolism or the intermediate metabolism of substrates. Larger studies will be needed to assess long term safety and efficacy.

Mauras N, et al. *Metabolism* 2002;51:127-135.

Editor's Comment: *This well designed study provides encouraging data that rhGH can overcome the anti-anabolic effects of prednisone, enhance the growth rate, and do so without measurable toxicity over 6-12 months. Of particular interest was the disappointing observation that there was no change in the disease activity as determined by the Crohn's Disease Activity Scale adapted for pediatric subjects. There were significant increases in serum levels of IGF-1 and IGF.BP3. The authors suggest that a state of "functional" GH deficiency caused by chronic steroids may be overcome with rhGH administration. It is important to remember that rhGH has not been effective in treating patients with IBD who are not on glucocorticoid treatment. Also of importance is to recall the reports of Rivkees et al and Allen et al who reported the acceleration of growth in glucocorticoid treated children with significant growth retardation who*

were treated with rhGH. Allen et al reviewed the data of the Genentech National Growth Study in which 83 children with extreme glucocorticoid induced short stature were treated for at least 12 months with rhGH. The authors concluded: (1) growth suppressing effects of chronic GC are counter-balanced by GH therapy; the mean response being a doubling of baseline growth rate, (2) responsiveness to GH is negatively correlated with GC doses, and (3) glycolysated hemoglobin levels increased slightly, but glucose and insulin levels were not altered by GH therapy. These authors summarized: "In a cohort of 83 poorly growing GC-dependent children, we suggest that the growth suppressing effects of GC can be variably overcome by GH. The short term risks of combined GH and GC treatment appear low; potential long term effects require further surveillance and study. Treatment of GC-dependent children with GH remains experimental; children considered for such treatment should be enrolled in studies that facilitate careful monitoring and data analysis." Dr. Mauras and her co-investigators have heeded the suggestion and extended the data. Rivkees et al, Allen et al, and Mauras et al are to be commended for clinical investigation that significantly enhances patient care.

Rivkees SA, et al. *J Pediatr* 1994;125:322-325.

Allen DB, et al. *J Clin Endocrinol Metab* 1998;83:2824-29.

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Inadequate Leptin Level Negatively Affects Body Fat Loss During a Weight Reduction Program for Childhood Obesity

These authors report findings of body fat loss in 37 female and 45 male overweight children, ages 10.9 ± 3.5 years, during a weight reduction program and correlated the weight loss with plasma leptin levels. The authors note that a large proportion (40-80%) of the variance in BMI can be ascribed to genetic factors; leptin appears to signal adiposity and leptin levels have not been shown to be predictive of successful weight loss. Leptin levels, although found to correlate positively with indices of general obesity, have not been found to be predictive for the success of weight loss in observational, longitudinal studies of dietary intervention. Some studies have shown that low serum leptin at baseline is associated with greater weight loss. Others have shown, in adolescents, that a greater baseline of leptin concentration correlates with weight reduction.

In the current study, fasting plasma leptin levels were determined and subjects were stratified on their leptin Z-score into low leptin (< -2 SD), high leptin ($\geq +2$ SD), or appropriate leptin (≥ -2 to $\leq +2$ SD), prior to their weight loss. Body fat was determined by BMI and skin

fold thicknesses. All subjects participated in a nutritionally balanced meal plan at 60% of the recommended energy allowances for age and sex. Physical activity was monitored, but no attempt was made to alter it. There were no significant differences in physical activity amongst the 3 groups of children stratified by fasting plasma leptin levels. Data was collected at 3 and 6 months which showed that 20 children had high leptin levels, 20 had relatively low leptin levels, and 42 fell in the appropriate leptin level range. There were no statistical differences among the three groups of children at baseline. Mean BMI and skinfold thickness at the end of 6 months were significantly lower than baseline data. BMI reduction was more evident in the subjects with adequate leptin levels but the differences were not statistically significant. Reduction in triceps and subscapular skin folds was also more pronounced in the appropriate leptin production group. The differences in the average of these changes were statistically significant after both 3 and 6 months.