

in the control children. During puberty, peak height velocity was not significantly higher in the GH-treated children than in the controls. The onset of the pubertal growth spurt was delayed in these children by approximately 2½ years (compared with normal children) and the duration of the growth spurt was 1.6 years shorter compared with that of normal children.

The total pubertal height gain was similar in the GH-treated and the control children, but was 65% of that in normal children because the pubertal growth spurt was shorter.

Catch-up growth was sustained in the GH-treated children whereas the control children had progressive growth failure. The standardized height increased from the baseline mean of -1.4 SD. The mean final height was 1.6 SD below normal in the treated group, whereas in the control children the standardized height decreased by a mean of 0.6 SD to a final mean adult height of 2.1 SD below normal. Sixty-five percent of the GH-treated children reached an adult height within the normal range, but the mean final adult height was approximately 10 cm below the genetic target height for boys and 12 cm below the genetic target height for girls. The final height in the control children was 15.8 cm lower than the genetic target in boys and 16.1 cm lower than the genetic target in girls. Although the bone age increased faster during the prepubertal period in the GH-treated children than in the controls, it did not reduce overall height gain. Multiple regression analysis revealed that the absolute as well as the standardized height gain during the observation period was significantly associat-

ed with the longer duration of the prepubertal and pubertal observation periods, a longer duration of GH therapy, a greater initial target height deficit, a lower percentage of time spent on dialysis, and male sex. These factors explain 61% to 87% of the variability in the outcome data.

The authors point out that this study provides evidence that GH treatment can sustain catch-up growth in the majority of children with growth failure due to chronic renal failure.

Haffner D, et al. *N Engl J Med* 2000;343(13):923-929.

Editor's comment: *This is a particularly important study because it is the first to look at final height achieved in this population. Clearly, GH therapy is of significant benefit to final height in children with chronic renal failure. The particular strengths of this study are the variety of causes of chronic renal failure in these children and the careful matching of the etiologies between the treated and control groups. An unanswered question is the effect of GH therapy on adult height in children who begin such treatment during their pubertal years. The data in the current study cannot be used to answer this question. The children in this study had glomerular filtration rates of <60 mL/min/m². It also will be important to evaluate the effect of GH therapy on children with lesser degrees of renal insufficiency but similar degrees of growth retardation.*

William L. Clarke, MD

The Impact of Recombinant Human Growth Hormone Treatment During Chronic Renal Insufficiency on Renal Transplant Recipients

Fine et al described the posttransplant outcome for renal transplant patients who were treated with GH therapy during the course of their chronic renal insufficiency. Subjects were identified from 2 control studies (n=194) and matched with patients in the North American Pediatric Renal Transplant Cooperative Study (NAPRTS) database; 95 "likely" matches and 7 "possible" matches were made. These 102 patients formed the GH-treated cohort group and were compared with a control group of 4913 transplant recipients in the database who did not receive GH therapy during their chronic renal insufficiency. Interestingly, the treated cohort tended to have more males, a larger percentage of subjects between 6 and 12 years of age, and more (67% vs 45%) living parent donors.

Two deaths occurred in the cohort, after 78 days and 5 years. The survival rate for the cohort at 3 years was 98.9%, while that for the control group was 95.1%. In the cohort group, 11.8% of grafts failed; 21% of the grafts failed in the control group. There is no statistically significant difference between graft survival rates for either donor source. The percentage of failed grafts with chronic rejection as the cause was marginally significantly higher than in the control group ($P=0.05$). However, the percentage of all grafts that failed as a result of chronic rejection was similar for the 2 groups (6.9 for the GH-treated cohort and 6.5 for the control).

The mean height Z score at 60 months was slightly improved in the treated group compared with a slight worsening in the control group. In both groups, the delta Z score was positive, indicating continued improvement from baseline. Adverse events in the treated cohort included 2 posttransplant lymphoproliferative disorders and 38 other events, including appendicitis, gastroenteritis, pneumonia, other infections, and hypertensive crisis.

There was no core of adverse events but a broad spectrum of unrelated events. The authors' data did not support the assertion that recombinant human growth hormone (rhGH) treatment during the course of chronic renal insufficiency predisposed to the development of malignancy after transplant.

The authors conclude that GH therapy was not associated with an increase in adverse effects on graft function, nor were there more malignancies posttransplantation. There were concerns that "catch-down" growth would occur after renal transplantation in individuals who received GH during renal insufficiency, which might nullify gains in height. These data do not substantiate these concerns.

Fine R, et al. *J Pediatr* 2000;136(3):376-382.

Editor's comment: The results are reassuring to physicians treating short children with chronic renal insufficiency with rhGH. Data from this study do not suggest a negative effect of such pretransplant therapy. Mean height scores in the treated group at baseline and 60 months posttransplant were -1.92 and -1.90 , as compared with the control group at -1.88 and -2.10 . Thus, gains made in height were not lost. This article and an accompanying article by Haffner et al (N Engl J Med 2000;343[13]:923-930) provide

significantly helpful and reassuring information regarding the safety and effectiveness of treating children with rhGH. The reader also is referred to a lead article in GGH (Vol. 12, No. 4, p 49) titled, "Recombinant Human Growth Hormone Therapy for Children With Chronic Renal Insufficiency: An Update 1996," which addressed the subject of rhGH treatment in chronic renal insufficiency.

William L. Clarke, MD

Treatment of Acromegaly With Pegvisomant, a Genetically Engineered Human Growth-Hormone Receptor (hGHR) Antagonist

The present investigators report the beneficial effects of a GH receptor (GHR) antagonist in adults with acromegaly. Genetic engineering has permitted development of a mutated GH molecule with replacement of 9 amino acids that increases its affinity for one of the binding sites on the receptor and abolishes binding to the second site, thereby preventing functionally correct dimerization of the receptor. Polyethylene glycol polymers, which are covalently bound to a protein, are stated to be pegylated, thus, the name pegvisomant. Since the GHR is unable to dimerize, signal transduction is inhibited, leading to decreased IGF-I production.

In short-term (12-week) studies, 112 acromegalic adult subjects who had failed previous treatment (surgery and/or radiation and/or dopaminergic agonists, but not long-acting analogues of somatostatin) were divided into 4 groups, including a control group and 3 groups receiving different doses of pegvisomant. IGF-I concentrations (Figure) fell in a dose-dependent manner. Symptoms of GH excess ameliorated as there were significant decreases in soft tissue swelling, diaphoresis, and fatigue. The score for total symptoms and signs of acromegaly decreased significantly in all groups receiving the drug. As expected, serum concentrations of GH increased substantially during treatment in the patients who received 15 or 20 mg of pegvisomant. Anti-GH antibodies were noted in 5 patients but were without physiologic consequence. No patient had a significant change in tumor volume during the study. One patient had alterations in liver function while receiving this agent. No serious adverse effects were otherwise noted. The long-term consequences of the elevated GH concentrations remain to be determined.

Trainer PJ, et al. N Engl J Med 2000;342:1171-1177.

Editor's comment: Neurosurgical removal of GH-secreting pituitary adenomas has been and remains the primary mode of therapy for acromegaly. Medical treatment of hypersomatotropism has been reserved as secondary management; estrogens, dopaminergic agonists (bromocriptine, cabergoline), and short- and long-acting somatostatin analogues (depot preparations of octreotide and lanreotide) that impair GHRH release and inhibit its function at the somatotroph membrane have been employed to lower GH production and decrease IGF-I generation. The introduction of a GHR antagonist has expanded the therapeutic boundaries for this disease, which is so difficult to treat. In another study,

