

Editor's comment: This report adds further data supporting the autoimmune etiology of acquired hypoparathyroidism in the majority of patients. The relationship of antibodies to the extracellular domain of the calcium sensing receptor in relation to the etiopathogenesis of acquired hypoparathyroidism is uncertain. In preliminary studies, the authors report that these antisera did not affect intracellular calcium levels in vitro in cells transfected with this receptor. These data indicate the need to study further the biologic activity of these antibodies and to search for other antigens that may be of pathophysiologic importance in this disorder.

Allen W. Root, MD

2nd Editor's comment: Exactly 30 years ago, Walter David, Darwin Chee, and I first reported the presence of parathyroid

antibodies in the sera of hypoparathyroid patients (Clin Exp Immunol 1966;1:119), as Li et al pointed out in their excellent article. Neufeld, Maclaren, and I then pursued over 15 years the theory that acquired hypoparathyroidism often was of autoimmune origin, but we and others had great difficulty in confirming our hypothesis in the laboratory. Li, Maclaren, and colleagues now have confirmed that autoantibodies exist against a specific component of the parathyroid cells. Observing this unraveling of questions and the near solving of the hypothesis over 30 years has been exciting and rewarding to me, and one of the pleasures and blessings of being given the opportunity to live and continue to be professionally active over such an extended period.

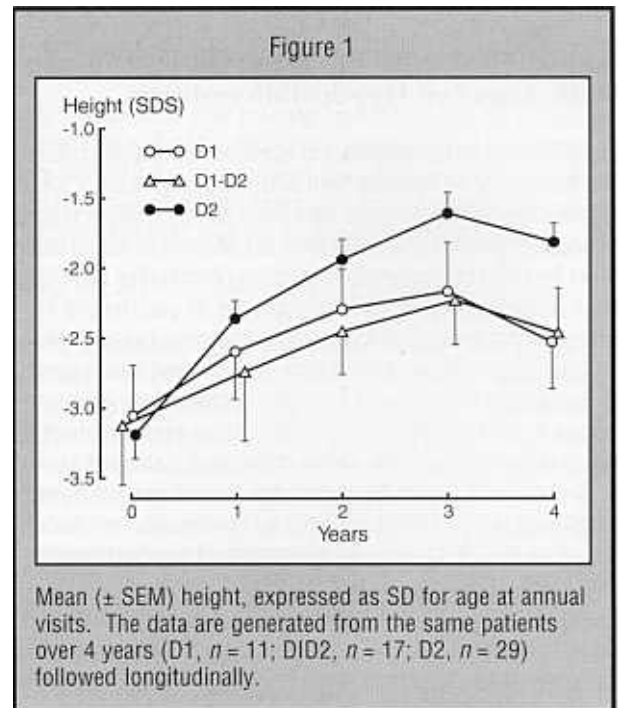
Robert M. Blizzard, MD

Follow-Up of Three Years of Treatment With Growth Hormone and of One Post-Treatment Year, in Children With Severe Growth Retardation of Intrauterine Onset

Job et al report follow-up data on their original randomized double-blind study of 2 doses of growth hormone (GH)—(0.4 IU/kg/wk (dose D1) or 1.2 IU/kg/wk (dose D2) (*J Clin Endocrinol Metab* 1994;78:1454-1460)—in prepubertal children with very short stature of intrauterine onset. Previously, they reported that growth velocity increased in intrauterine growth retarded (IUGR) children treated with GH in a dose-dependent manner. At the end of 2 years of GH treatment, subjects receiving the low dose of GH (D1) were randomized either to continue the same dose or be switched to the higher dose (D1D2) and treated for an additional year. Finally, a follow-up year of no GH treatment was added to their study. Seventy-eight subjects were studied. Both birth length and birth weight had to be -2 SD or more below the mean for gestational age; height at admission had to be -2 SD or more below the mean according to the usual French standards; bone age had to be either retarded or equal to the chronologic age; and the growth velocity for the previous 12 months could not exceed the mean for age. In addition, all patients had to be prepubertal. Height and sexual development were assessed every 3 months during GH treatment and every 6 months during the posttreatment year at 10 different centers in France and Belgium. In addition to careful height and weight measurements and assessment of sexual development, bone age was determined by the method of Gruelich and Pyle every 6 months. Sixty-six children remained in the study at follow-up.

Average age at the onset of the study in 1988 was 8.1 ± 0.2 years. The mean annual height velocities were greatest during the initial year of GH treatment and subsequently declined. At the end of 3 years of treatment, the height reached -2.37 SD in D1, -2.17 in D1D2, and -1.58 in D2 (Figure 1). The total height gain was 0.77 ± 0.1 SD in D1, 0.93 ± 0.15 SD in D1D2, and 1.61 ± 0.08 SD in D2. The percentage of children whose height was within the normal range for age was 46.7% in D1, 52.2% in D1D2, and 70% in D2.

During the follow-up year without treatment, growth deceleration was observed in most patients, with mean growth velocity falling below -1 SD. The mean loss in height was approximately 0.25 SD for age. Skeletal maturation over 36 months of GH treatment was not significantly different among the 3 groups. Mean bone age, however, remained retarded in all 3 groups at the end of the fourth year of study. There were no significant differences among the 3 groups in the frequency of occurrence of puberty or in age at its onset; the rate of sexual maturation after its onset did not differ among the groups.



The authors state that their data confirm that GH treatment can accelerate the growth of IUGR short children beyond 2 years of treatment despite "the waning effect" of GH and that this growth is accompanied by some degree of acceleration in bone maturation. The authors note that the strengths of their study include: (1) the cohort, which excluded familial short stature but did include 6 cases of Silver-Russell-type dwarfism, was homogeneous; (2) puberty began within the normal age range; and (3) they included the growth velocity after discontinuation of GH treatment. There are no data, however, on final heights.

Job JC, et al. *Pediatr Res* 1996;39:354-359.

Editor's comment: *This is a very interesting paper. Job et al have performed an evaluation of long-term use of GH in IUGR short children. It would be of interest to have more*

information with regard to the range of bone age retardation in the patients when initially seen. With mean heights at the end of the study averaging from -1.8 ± 0.2 SD to -2.5 ± 0.4 SD and bone age being delayed approximately 1 year or more, it is unclear whether a significant number of these children also have constitutional delay of growth and adolescence. In addition, the inclusion of children with Russell-Silver syndrome may have adversely affected the growth response data. However, the authors are to be congratulated in carrying out such a long-term study and including a year of follow-up. It would have been interesting to have included a control population of similarly height-challenged IUGR patients who were not treated and were of similar age. We would hope Job and colleagues will continue their studies and report final heights in these patients in the next few years.

William L. Clarke, MD

The Relation of Transient Hypothyroxinemia in Preterm Infants to Neurologic Development at Two Years of Age

Taking advantage of the prospective design of the Central New Jersey Neonatal Brain Hemorrhage Study, this retrospective study was performed in a historical cohort. The authors chose those infants who were born at 33 weeks of gestation or earlier, who had undergone screening for congenital hypothyroidism within the first 7 days of life, and who survived until the age of 2 years or beyond ($n=536$; Figure 1). The levels of thyroxine were retrieved from the newborn screening program and were expressed as a SD score (SDS) to correct for the daily interassay variation. Severe hypothyroxinemia was defined as a blood thyroxine value more than 2.6 SD below the mean for New Jersey newborns. None of the infants had congenital hypothyroidism.

Neurologic and developmental outcomes were assessed at 2 years of age by means of the Bayley Psychomotor Developmental Index and the Bayley Mental Developmental Index or the Stanford-Binet Intelligence Scales for Children. Emphasis was placed on the presence of disabling cerebral palsy and/or low mental developmental scores. Twenty-two prenatal, perinatal, and early neonatal variables were analyzed in order to adjust for any association between hypothyroxinemia and a given neurodevelopmental outcome. Infants with severe hypothyroxinemia had a risk of disabling cerebral palsy that, depending on the extent of adjustment for covariates, was 4.4 to 17.6 times that of the infants with normal thyroxine concentrations. The mental development scores at 2 years of age were 8 to 18 points lower in infants who had had severe hypothyroxinemia than in those with normal thyroxine levels. The authors conclude that severe hypothyroxinemia in preterm infants may be an important cause of problems in neurologic and mental development detected by 2 years of age.

Reuss ML, et al. *N Engl J Med* 1996;334:821-827.

