

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  $-1.8 \pm 0.2$  SD to  $-2.5 \pm 0.4$  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.

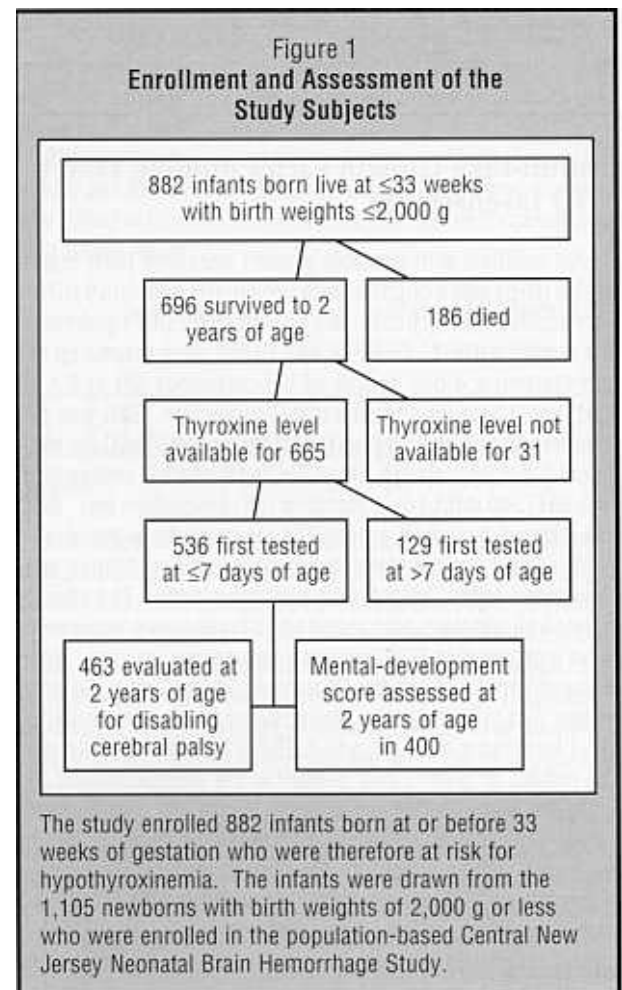
William L. Clarke, MD

## 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.



**Editor's comment:** This paper is very important as it provides data indicating that transient hypothyroxinemia without hyperthyrotropinemia in preterm infants is not benign. The study by Reuss et al rings a bell of alarm and prompts us to approach these infants more carefully. The mechanism of transient hypothyroxinemia in preterm infants, however, has not been elucidated. It may involve either a metabolic adaptation to nonthyroidal illness or an incomplete maturation of the hypothalamic-pituitary-thyroid axis as discussed by Vulmsa and Kok<sup>1</sup> in the editorial comments that accompanied the paper.

The traditional belief that the fetus does not need thyroxine for intrauterine development was based on the assumption that negligible amounts of thyroxine from the mother crossed the placenta. This belief was first challenged when significant passage of thyroxine from the mother to the fetus was identified, and it is now being challenged again with the findings of Reuss et al of poor mental and developmental outcomes of preterm infants displaying transient hypothyroxinemia. Treatment of these infants aiming to correct the subnormal levels of thyroxine as soon as detected will be the next step, but this should be undertaken only in a controlled study.

Fima Lifshitz, MD

1. Vulmsa T, Kok JH. *N Engl J Med* 1996;334:857-858.

**2nd Editor's comment:** Having just reviewed this abstract and Dr. Lifshitz's editorial comment, I attended The Endocrine Society meeting in San Francisco and read an abstract by Dr. M.K. Hunter et al entitled, (Program, 10th IC of Endocrinology, Vol II: June 14 and 15, 1996, OR 48-4, page 7113). Follow-up of Newborns With Low T<sup>4</sup> and Non-Elevated TSH Concentrations. The content of the abstract was related to the article by Reuss et al. Therefore, the important comments and data follow:

Over a 20-year period, the Northwest Regional Screening Program screened 1,747,805 newborn infants. Follow-up of infants with low thyroxine levels without thyrotropin (TSH) elevation led to the diagnosis of hypothyroidism in 60, including 25 infants with delay in TSH rise (1:67,226 infants), 9 infants with mild hypothyroidism (TSH <25 IU/L), and 26 infants with hypopituitary hypothyroidism (1:67,223), in addition to 4,334 infants with thyroid-binding globulin deficiency (1:4,027). Follow-up was scheduled at 1 year of age.

These data indicate that follow-up of infants (preterm or term) with low thyroxine and normal TSH levels is important.

Robert M. Blizzard, MD

## Insulin-Like Growth Factor Binding Protein-3 Generation: An Index of Growth Hormone (GH) Insensitivity

Eleven children with possible growth hormone (GH) insensitivity (GHI) and 8 children with proven GH deficiency (GHD) were studied with an insulin-like growth factor (IGF) generation test in which IGF-1, IGFBP-3, and GHBP were measured before starting a 4-day course of subcutaneous GH at 0.1 U/kg/d, and 12 hours after the last GH injection. GHI was defined based on short stature for target height (-2 SD for mid-parental height), a high basal GH (>10 mU/L), and/or high peak GH (>40 mU/L) on a standard GH provocation test. GHD was defined based on a peak GH response to arginine ≤10 mU/L. The 2 groups were comparable in terms of their age, body mass index, height, and growth velocity. The change in these parameters was analyzed as an absolute increment, as an increment in SDS, and as a percentage change. None of the children fulfilled the Pharmacia Study Group IGF generation test criteria for the diagnosis of Laron syndrome; ie, IGF-1 increment <15 µg/L and IGFBP-3 increment <0.4 mg/L. The results of ΔIGF-1 and ΔGHBP in the generation test did not show statistical differences (ie, could not discriminate) between the GHI and the GHD patients regardless of whether the results were analyzed as absolute change, as percentage increment, or SDS increment. However, the results of IGFBP-3 showed statistical differences between the 2 groups of patients when comparing the poststimulation peaks by increment as well as the percentage increments. Significant *inverse*

correlations were found between peak GH obtained during provocative tests. Both the IGF-1 and IGFBP-3 rose in the IGF generation test. Percentage increase of IGFBP-3 was identified as the most significant parameter to predict GH peak by stepwise multiple regression analysis.

The authors speculate that some children may have selective resistance in either the GH-IGF-1 axis or the GH-IGFBP-3 axis, given the varied combination of responses found in the study. IGF-1 generation per se was inadequate as an index of partial GHI and should be used in conjunction with IGFBP-3 generation.

Thalange NKS, et al. *Pediatr Res* 1996;39:849-855

**Editor's comment:** Bioinactive GH secondary to mutations of the GH gene<sup>1</sup> and GH receptor mutations associated with clinical pictures of partial GHI<sup>2,3</sup> (see GGH vols 11:4 and 12:1, respectively) have been recently identified. Although these newly described and documented entities definitely are helping us understand the different pathophysiologic mechanisms of short stature, accurate diagnosis can be made only with sophisticated technology. Their clinical recognition continues to be elusive. This paper by Thalange et al attempts to identify easily available biochemical markers in the context of dynamic testing, which may yield a diagnostic clue in identifying patients