

Increase of Serum Lipids and Serum Lipoproteins in Girls on Therapy With Estrogen and Norethisterone for Height Reduction

Weninger et al measured the levels of serum cholesterol and triglycerides in 23 tall girls, ages 11.2 to 15.5 years (mean 12.7 ± 1.1) whose height was 2 to 4.2 standard deviation scores above the mean for age, prior to and during therapy with a combination of ethinyl estradiol (0.5 mg/day orally) and norethisterone (10 mg/day on days 21 to 25). These patients were followed for 11 to 24 months.

Serum cholesterol and triglyceride levels rose significantly (cholesterol, 4.27 ± 0.93 mmol/L v 5.33 ± 0.65 , $P < 0.001$; triglyceride, 0.95 ± 0.28 mmol/L v 1.82 ± 0.57 , $P < 0.001$) after three months of therapy. In a subgroup of 11 girls, low-density and high-density lipoprotein levels were determined; both rose significantly above baseline values after three months of treatment.

These investigators also evaluated the effect of norethisterone on the serum cholesterol and triglyceride concentrations immediately before and after five days of administration. No immediate effects of norethisterone were evident. After the cessation of all therapy, elevated lipid levels returned to pretreatment levels within 3 to 12 months in all but two patients.

The authors point out that the observed increase in lipids and lipoproteins during therapy for tall stature is in contrast to the physiological decrease in lipids that occurs during adolescence. Therefore, they conclude that therapy rather than sexual maturation is responsible for the lipid and lipoprotein changes they observed.

Weninger M, Frisch H, Schober E, et al. *Acta Paediatr Scand* 1987; 76:500-503.

Pubertal Development in Male Hypopituitarism

In hypopituitary adolescents, puberty takes a different course than it does in normal individuals, patients with hypogonadotropic hypogonadism, and those with isolated growth hormone deficiency (IGHD).

Martinez et al analyzed the course of sexual maturation in 65 male patients with hypopituitarism who were treated at the Hospital de Niños in Buenos Aires between 1965 and 1982. Eighty-two percent of the children with IGHD and 32.5% of those with multiple pituitary hormone deficiencies (MPHD) experienced spontaneous puberty. Thirty-six patients

were followed longitudinally. Fifteen showed spontaneous sexual development commencing at a chronological age (CA) of 15 years, 3.2 years later than in normal Argentinian boys. Mean bone age (BA) was 10.4 years. There was no difference in BA between patients with IGHD and MPHD. Plasma testosterone was slightly but not significantly higher in these patients than in the controls.

Eleven of the 15 patients received human growth hormone (hGH) continuously; four could not be treated. Peak height velocity was 7.49 ± 1.7 cm/year in the treated subjects and 6.67 ± 2.3 cm/year in the untreated ones. Mean CA of the 21 subjects with MPHD whose sexual maturation

Editor's comment—*Treatment of tall stature with estrogen has been used for several decades. Usually, the therapy is reserved for girls who are experiencing significant psychological problems because of tall stature. It has been stated that the earlier treatment is begun, the greater the reduction in adult stature. It has been well documented that height reduction can be achieved. However, there are numerous side effects associated with treatment. Do the benefits of treatment justify the risks?*

Weninger et al have observed a marked increase in serum lipids and lipoproteins during combined estrogen and norethisterone treatment for height reduction in tall girls. Although this increase is transient, reverting to pretreatment values once therapy is concluded, the long-term effects of elevated lipids cannot be known at this time. Pediatric endocrinologists are cautioned that hormonal therapy for height reduction in tall girls may not be without significant risk and should be reserved for patients for whom counseling is not effective. The side effects described here should be discussed with the parents before initiating therapy.

William L. Clarke, M.D.

Long-Term Monitoring of Treatment With r-hGH by Serial Determinations of Type III Procollagen-Related Antigens in Serum

The measurement of type III procollagen (P-III-NP) by two radioimmunoassays before and during treatment with human growth hormone (hGH) in 20 patients with GH deficiency was reported. One assay (RIAgnost assay) recognized the intact propeptide predominantly. The second (FAB assay) recognized both the intact propeptide and a smaller monomeric peptide.

In childhood, P-III-NP levels vary with age and correlate significantly with the growth velocity curves. In the 20 GH-deficient patients studied by the authors, P-III-NP and somatomedin-C (Sm-C) levels increased after three days of recombinant hGH (r-hGH) therapy (2 IU/m², six or seven days per week). The values increased within one month to those usually seen in healthy children, but Sm-C levels did not increase above the values seen at three days.

Only two parameters—lower

was induced by gonadotropin was 19.04 ± 2.2 years at start of treatment, while BA was 12.94 ± 0.8 years. Plasma testosterone reached physiological values quickly, except in two patients who showed no response. Mean growth velocity of the patients who simultaneously received treatment with hGH was 6.11 cm/year and only 4.91 cm/year in those who did not receive hGH.

Martinez AS, Heinrich JJ, Rivarola MA, Bergadá C. *Eur J Pediatr* 1986;145:384-388.

Editor's comment—*The observations confirm the often-published experience that the less global the central lesion is, the more*

frequently spontaneous puberty occurs. The retardation of spontaneous puberty in the non-hypogonadotrophic patients amounted to 3.2 years over healthy Argentinian boys. BA, however, corresponded to the standard of normal boys at start of puberty. Growth velocity was within the normal range in these boys. However, the observation that patients who did not receive GH also had high growth velocities appears to be remarkable. Their mean height velocity amounted to 6.67 cm/year, a value slightly but not significantly below that of the hGH-treated boys. For patients with GH deficiency, this value is surprisingly high.

Jürgen R. Bierich, M.D.

skeletal age and higher basal P-III-NP values as determined by the RIAGnost assay—studied during the pretreatment period proved to be associated with height increase after six months of therapy. Both seemed to have predictive relevance to growth velocity. Levels of basal Sm-C, alkaline phosphatase, or P-III-NP (by FAB assay) did not have predictive relevance for growth velocity during this period. The increases of P-III-NP levels following three days or one month of GH treatment did not correlate with the increase observed in growth velocity during the six months of treatment.

P-III-NP serum antigens measured by both assays correlate with each other but provide different information. The RIAGnost method recognized intact propeptide and may be more sensitive than the FAB assay in reflecting unstimulated basal collagen metabolism. The authors postulate that the correlation between the normal P-III-NP values obtained by the RIAGnost assay before treatment and the subsequent growth response indicates that reasonable normal collagen synthesis may be a prerequisite for a satisfactory growth response to

hGH. The authors further postulate that this is important because hGH is proposed as possible therapy for diseases in which disturbances of connective tissue or bone metabolism are suspected, such as in Turner syndrome. In patients with Turner syndrome, low basal levels of P-III-NP are reported, and the growth response to hGH is not as striking as that observed in patients with GH deficiency.

Danne T, Gruters A, Schnabel K, et al. *Pediatr Res* 1988;23:167.

Editor's comment—*A marker to determine the propensity of various patients to grow well when hGH is administered is very much needed. A better understanding of the roles of various types of collagen in the growth process and their controlling factors, such as hGH, is also much needed. Danne et al have the methodology that permits them to begin the study of such phenomena. The importance of this article remains unknown, but it is presented because of its potential therapeutic implications and its succinct review of what is currently known about the effect of hGH on collagen synthesis.*

Robert M. Blizzard, M.D.

Growth of 519 Small-for-Gestational-Age Infants During the First Two Years of Life

Tenovuo et al have carefully followed the physical growth of 519 small-for-gestational-age (SGA) infants for a period of two years. SGA infants were defined as those below the tenth percentile on growth curves generated at the authors' institution. These infants were compared to 4,517 term infants whose length and weight were appropriate for gestational age. The authors used the Rohrer's Ponderal Index (PI)

$$\frac{\text{weight (g)}}{\text{length}^3(\text{cm})} \times 100$$

to classify the SGA infants.

Infants who were small with respect to weight and length (Type I intrauterine growth retardation [IUGR]) tended to have a normal PI, while those who were small with respect to weight only or who had disproportionate growth had a low PI. The latter infants have type II, or disproportionate, IUGR.

Approximately 92% of the SGA infants and 94% of the control infants took part in the follow-up study two years after birth. In addition to the comparison studies between the two groups, the authors utilized stepwise logistic regression analysis for determining variables, such as maternal smoking and toxemia, that might best explain the small neonatal size.

The findings demonstrate that SGA infants with a low PI were taller and had a larger head circumference at age 24 months than the term infants with a normal PI. Among preterm SGA infants, the degree of IUGR appeared to have no effect on later growth. The catch-up growth in SGA infants occurred in the first three months after birth although they remained significantly smaller than the control infants.

The type of IUGR affects later growth. Type II IUGR infants (PI

continued on page 14