

GH during puberty, when GH release in the normal adolescent is stimulated by sex steroid secretion.

The sixth presentation was entitled, *Catch up Growth and Height Achievement in Older, Late-Treated GHD Patients* (OR 46-6). It pertained to GHD children >15 years of age who were minimally or not sexually developed when treatment was instituted.<sup>6</sup> Their mean bone age was  $12.2 \pm 1.8$  years. Year 1, 2, and 3 growth rates with treatment were  $8.5 \pm 3.1$  cm,  $7.2 \pm 2.3$  cm, and  $6.0 \pm 2.0$  cm, respectively. The conclusions were that over the 3 years, improvement of height age ( $3.2 \pm 1.2$  years), height SDS ( $2.3 \pm 1.1$  SD), and Bayley-Pinneau predicted height ( $0.9 \pm 1.4$  SD) were observed. Two patients over 20 years of age, who were sexually infantile, responded similarly.

The seventh paper was from a collaborative European study, entitled *Four Years of GH Therapy in 3 Dosage Regimens in 216 Children With ISS* (OR 46-7).<sup>7</sup> The conclusions were that GH at 3.0 or 4.5 IU/m<sup>2</sup> (1.0 to 1.5 mg/m<sup>2</sup>) resulted in a doubling of the height velocity during the first year. Increasing the dosage after the first year (3.0 to 4.5 IU/m<sup>2</sup>) reduced the waning growth effect. Growth and final height prognosis improved during 4 years of GH therapy. This was better with 4.5 IU/m<sup>2</sup> than with 3 IU/m<sup>2</sup>.

The eighth presentation, a report from European collaborators, dealt with long-term response to rhGH treatment in Turner syndrome (OR 46-8). One hundred ninety patients were studied. The Europeans concluded that a 5.0-cm increment (corrected) was added with GH treatment, with wide individual variation. A significant discussion ensued regarding the effect and necessity of beginning GH therapy earlier than the  $\geq 9$  years of age (average) for patients in the reported study.

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1. Woods KA, et al. Department of Endocrinology, St. Bartholomew's Hospital Medical College, London.
2. Maheshwari H, et al. Department of Medicine & Pediatrics, Northwestern University Medical School, Chicago.
3. Fiallo RV, et al. Department of Pediatrics, New York Hospital-Cornell Medical Center, New York.
4. Laron Z, et al. Department of Pediatric Endocrinology, Tel Aviv University.
5. Blethen SL, et al. Department of Pediatrics, SUNY, Stony Brook, New York.
6. Brasel JA, et al. Harbor UCLA Medical Center, Torrance, California.
7. Mombarg LTM, et al. Department of Pediatrics, University Hospital, Leiden.
8. Van der Boeck J, et al. Department of Pediatrics, Academic Hospital, Leiden.

#### Abstracts From the Literature

### Short Stature Caused by a Mutant Growth Hormone

The authors studied a 4.9-year-old boy with short stature (height, -6.1 SD below mean for age and sex) whose growth was normal in utero. Basal and stimulated secretion of immunoreactive growth hormone (GH) was normal but levels of bioactive GH were subnormal. He responded to the administration of GH with an increase in growth rate. Isoelectric focusing was performed, and 2 GH peaks were detected in the proband in comparison to 1 peak in normal subjects. Examination of the *GH-1* gene revealed a heterozygous mutation (guanine to cytosine transversion) of 1 GH gene allele at codon 77 in exon 4, with substitution of cysteine for arginine. This mutation is near a controlling point for the binding of GH to its receptor. Thus, the patient had 2 species of GH, 1 wild-type and 1 mutated form. A similar heterozygous mutation was found in the father, who was of normal height but who had 1 serum GH peak by isoelectric focusing. Further analysis of the mutated GH expressed in *Escherichia coli* revealed that it had normal immunoreactivity compared with wild-type GH, but that it bound to the extracellular domain of the GH receptor (ie, the GH-binding protein) 6-fold more avidly than did native GH. Since this mutated GH did not stimulate intracellular signaling pathways in IM-9 cells, which have GH receptors, it inhibited the biologic effects of wild-type GH in this system. The investigators suggest that the mutated form of GH impaired growth by antagonizing the effects of the native GH molecule, which was also synthesized and secreted by the patient. The reason why

the father with the same heterozygous mutation in the *GH-1* gene did not express this abnormal allele was unexplained.

Takahashi Y, et al. *N Engl J Med* 1996;334:432-436.

**Editor's comment:** In the last few months there has been great interest in children with idiopathic short stature (ISS). Partial GH insensitivity among patients with ISS was described earlier (*J Pediatr* 1995;127:244-250, published in abstract form in *GGH Vol 11*[4]:8). This was followed by the description of specific mutations of the GH receptor gene associated with ISS (*N Engl J Med* 1995;333:1093-1098, published in abstract form in *GGH Vol 12*[1]:14 & 15). Now, Takahashi et al describe a mutation in the GH gene itself that produced an abnormal GH and was clinically associated with short stature in the affected individual.

These papers provide data heralding a new subset of patients in whom GH gene mutations or GH receptor abnormalities explain the bioinactivity of GH. The prevalence of these abnormalities in children with ISS is unknown. Moreover, the features that clinicians should follow to identify GH insensitivity or bioinactivity also are not clarified. The diagnosis of these conditions continues to be based upon esoteric, highly sophisticated biochemical assessments.

Fima Lifshitz, MD

**2nd Editor's comment:** Long sought but heretofore undiscovered, the elusive bioinactive GH molecule has now been identified in 1 patient. Previously, many patients have been suspected of having a biologically inactive, but immunologically active, GH (Kowarski et al, 1978; Valenti et al, 1985; Hayek et al, 1978; Bright et al, 1983; and others). However, with the technology of the 1970s and 1980s, it was not possible to prove that such a syndrome exists. Isoelectric focusing, studies of gene structure, and the interest and expertise of these authors have made

the suspected syndrome a fact. They clearly demonstrated that the proband synthesized and secreted an atypical form of GH that was able to bind with high affinity to the extracellular domain of the GH receptor, was unable to initiate signal transduction, and inhibited the biologic effects of native GH. The failure of the father with the same heterozygous mutation to express this phenotype demands further consideration.

Allen W. Root, MD

## Effects of Recombinant Human Growth Hormone (rhGH) Treatment in Intrauterine Growth-Retarded Preterm Newborn Infants on Growth, Body Composition and Energy Expenditure

The investigators from Amsterdam administered rhGH (1.0 IU/kg or 0.33 mg/kg/d) to 7 preterm infants (mean gestational age, 30.4 weeks) with IUGR (mean birth weight, 938 g) beginning at 7 days of age and continuing until achieved weight was 2,000 g (34 to 68 days of treatment). When compared with an untreated control group of IUGR preterm infants, there was no effect of rhGH on: time to doubling of birthweight; increments in body weight, length, and head circumference; ponderal index; serum glucose or insulin values; skin-fold thicknesses; total body water; or energy expenditure. The authors concluded that administration of rhGH had no effect on growth or energy metabolism in preterm infants with IUGR.

**Editor's comment:** Despite some problems with the applicability to IUGR preterm infants of the utilized methodology<sup>1</sup>, the data are of interest because they indicate that even exceedingly high doses of rhGH cannot positively affect the growth or metabolism of such children. Whether such therapy can have adverse effects is unknown at present. The findings also indicate the need to search for growth factors other than rhGH (perhaps insulin-like growth factor 2, insulin, etc) that may be of benefit to IUGR preterm infants. The utility of rhGH in preterm infants with appropriate growth for gestational age has yet to be assessed.

Allen W. Root, MD

an Toledo-Eppinga L, et al. *Acta Paediatr* 1996;85:476-481.

Wollmann H, et al. *Acta Paediatr* 1996;85:398-400.

## Prenatal Diagnosis of 45,X/46,XX Mosaicism and 45,X: Implications for Postnatal Outcome

Prenatal diagnosis of chromosomal abnormalities is available for families who have an option whether to continue the pregnancy. Twelve patients with 45,X/46,XX mosaicism were diagnosed prenatally by amniocentesis and subsequently evaluated at 3 months to 10 years of age. All have had normal linear growth. Four had anomalies, including esotropia and ptosis (1); labial fusion (1); atrial septal defect (1); and urogenital sinus, dysplastic kidneys, and hydrometrocolpos (1). The patient with ophthalmologic abnormalities is mentally delayed. None would have warranted karyotyping for clinical suspicion of Turner syndrome. These 12 were compared with 41 45,X/46,XX patients diagnosed postnatally. The prevalence of 45,X/46,XX mosaicism is 10-fold higher among amniocenteses than in series of postnatally diagnosed individuals with Turner Syndrome, which suggests that most individuals with this karyotype escape detection and that an ascertainment bias exists toward those with clinically evident abnormalities. The authors note that the phenomenon of a milder phenotype for the prenatal group is similar to that observed for 45,X/46,XY individuals diagnosed prenatally. The

authors emphasize that prenatal counseling for 45,X/46,XX in the absence of such ultrasound abnormalities as hydrops fetalis should take into account the expectation of a milder phenotype than that of patients ascertained postnatally. The same does not hold true for 45,X diagnosed prenatally.

Koeberl DD, et al. *Am J Hum Genet* 1995;57:661-666.

**Editor's comment:** This presentation provides important information for genetic counseling. One should not be too discouraging when discussing the expectations of a fetus when a 45,X/46,XX karyotype or a 45,X/46,XY karyotype is reported. Many of these 45,X/46,XX children will be phenotypically normal and possibly may end up with a 46,XX karyotype. The 45,X cell line may sometimes disappear, although that was not investigated in this study. This comment is made because the prevalence of 45,X/46,XX mosaicism is 10-fold higher among amniocenteses data than in series of postnatally diagnosed individuals with Turner syndrome.

Judith G. Hall, MD