

Pituitary Dwarfism in a Patient With Circulating Abnormal GH Polymers

Valenta et al describe the growth pattern of a short 14-year old boy, the son of relatively short parents. His height and weight were average for a 10-year-old, and he had growth failure for at least the previous three years, growing between 1.5 and 3.5 cm/yr. Despite Tanner stage III development of the genitalia and pubic hair and circulating sex-hormone levels corresponding to this stage of sexual development, he had not yet shown a pubertal growth spurt. The physical examination, blood chemistry analyses, and circulating pituitary and endocrine target organ hormone concentrations were normal. The responses to all pharmacologic stimuli for growth hormone (GH) secretion were normal (peak GH: 9.6 to 36 ng/ml) and the somatomedin C (SmC) concentration was 1.7 U/ml. There was a marked

acceleration of growth rate during exogenous GH therapy.

The circulating GH and the fractionated components (gel chromatography) were subjected to various immunoassays and bioassays to determine their activities. Using the IM-9 continuous cell line of cultured human lymphocytes (receptor assay, RRA), these investigators found an RRA/radioimmunoassay of 0.5 and the bioassayable activity (Nb-2 cell lactogenic assay) reduced by 25%. On column chromatography, the usual three peaks of GH species were noted—"Big-Big" [85,000 Daltons, (?) tetramer], "Big" [45,000 Daltons, (?) dimer], and "little" [20,000 Daltons, monomer]—but were present in unusual proportions—60% to 90% GH polymers rather than the more usual

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14% to 40% in plasma. Further physical analysis revealed that the units of the polymers were joined by disulfide (covalent) linkage rather than the more usual noncovalent ("stuck together") forces.

Valenta LJ, Sigel MB, Lesniak M, et al: *N Eng J Med* 1985;312:214.

Editor's comment—*The chemical analysis of the circulating GH species is very thorough and makes a very convincing case for a distinct abnormality in the physical and chemical properties of GH. However, it is less certain whether these abnormalities were the cause of this young man's shortness.*

From the few growth points mea-

sured early on, it seems likely that this boy did not have growth failure before the age of 8 or 9 years. This pattern would be distinctly unusual for a congenital growth problem. In addition, the baseline SmC concentration was at the upper limit of normal—1.7 U/ml—rather than subnormal, which would be the case if these molecular species were unable to cause the liver to produce SmC. The IM-9 cell receptor GH activity was low with respect to the immunoassay potency, but no mean and standard deviations are given for those GH components in normal serum. Could these values merely represent the "tail" of Gauss? Finally, the Nb-2 cell bioassay results reflect the lactogenic activity of circulating human growth hormone

(hGH) (after immune precipitation of the other lactogen, prolactin). Although the results may be low (no mean and standard deviations are given for normals), this activity may not reflect the growth-promoting activity of hGH. What clearly needs to be done with the GH molecules in this patient's serum is to concentrate them immunologically before testing the mixed and/or separated components in a bioassay for growth in hypophysectomized mice or rats or in the tibial-line assay. In summary, although this patient most probably has an abnormality in distribution of GH polymers, it is doubtful that the hypothesis of an abnormal circulating GH molecule of diminished biological activity has been proven.