27 The Role of Cyproterone Acetate in the Treatment of Isolated Growth Hormone Deficiency.

Kenji Ohyama, Masatoshi Fujimoto and Kiyohiko Kato
Department of Pediatrics, Yamanashi Medical College, Yamanashi 409-38, Japan

In isolated growth hormone deficiency(i-GH-def) treated with GH, disproportinately advanced bony maturation occasionally followed in early to mid stage of puberty. We studied the effect of cyproterone acetate(CA) on accelerated sexual maturation associated with GH therapy for i-GH-def. Subjects were 7 patients, ages 14-19 years, and 2 females and 5 males. Four of them received 100mg/m²/day of CA for 1 to 3 years. In all, secondery sexual maturation occurred at 13 to 16 years of chronological age and at 9 to 13 years of bony age(BA). Serum testosterone(T) levels rapidly increased at 2nd grade of Tanner in male patients (T:530 -1560 ng/dl). In 3 males without CA treatment, bony maturation advanced rapidly from 2nd to 3rd grade of Tanner and a sensitive period for GH therapy was shortened. After a combined therapy of CA and GH, bony maturation decelerated and serum T levels fell off to prepubertal level(<30 ng/dl). Two females treated with CA exhibited the similar effect. Serum somatomedin-C responses to GH were similar before and after the CA therapy. A ratio of Δ height age/Δ BA for first one year after an appearance of secondary sexual characteristics was below 0.5 in 3 patients without CA treatment, but the ratio reached 1 or above in all of 4 treated with CA. In i-GH-def, CA suppressed the advance of Bony maturation and prolonged the effective period of GH therapy, and consequently may be able to make final height heigher than predicted adult height before CA treatment.

28 GROWTH HORMONE (GH) SECRETORY PATTERNS IN CHILDREN WITH SHORT STATURE.

Gertrude Costin and Francine R. Kaufman. Univ. of So. Calif., Sch. of Med., Dept. of Peds., Los Angeles, Calif, U.S.A.

Thirty-six healthy children, 2½ - 16½ years old, (26 males, 10 females) with short stature, subnormal rate of growth and stimulated GH levels > 7 ng/ml, had measurements of GH every ½ hr for 24 hr. Based on the 24 hr GH concentration, the patients (pts) were separated into 2 groups of 18. The 24 hr GH concentration was normal (> 3.0 ng/ml; B.E. Spilliotis et al, JAMA 1984) in all pts in gr I and abnormal in all gr II pts. The mean (± SEM) 24 hr GH concentration, the number of GH pulses/24 hr and the mean peak GH amplitude were significantly greater ($p < 0.05$ to $p < 0.0005$) in gr I (4.08 ± 0.23; 4.6 ± 0.3 and 7.2 ± 0.35) than the corresponding values in gr II (2.31 ± 0.09; 2.27 ± 0.34 and 4.4 ± 0.33). The mean highest stimulated GH level in gr I was 20.1 ± 1.7 ng/ml (range 12.5 - 39.5 ng/ml) and significantly greater ($p < 0.01$) than the level of 14.5 ± 1.13 ng/ml (range 9.5 - 25.5 ng/ml) in gr II. In pts in gr I the mean 24 hr GH concentration and the number of GH pulses/24 hr were significantly greater ($p < 0.05$; $p < 0.0005$) in pubertal (4.61 ± 0.45; 5.62 ± 0.37) than in prepubertal pts (3.65 ± 0.12; 3.8 ± 0.24) but no differences were noted in pts in gr I. SmC levels ranged from 0.14 to 1.5 U/ml in gr I and from 0.10 to 1.8 U/ml in gr II. No significant differences in SmC levels were found between the 2 groups, however, in both groups the mean SmC level was greater in pubertal than in prepubertal pts.

The results indicate that 1) abnormalities in neuroregulation of GH secretion may be a common cause of short stature, 2) GH responses to provocative stimuli and SmC levels are not diagnostic of subtle abnormalities in GH secretion and 3) puberty may augment GH release in children with normal 24 hr GH concentration but appears to have no effect in children with disturbances in GH secretion. Growth response to hGH therapy may elucidate whether dysregulation in GH secretion is a treatable cause of short stature.

29 DECREASE IN CYTOCHROME P-450 DEPENDENT 3-N-DEMETHYLATION OF CAFFEINE MEASURED BY THE CAFFEINE $^{13}CO_2$ BREATH TEST (CBT) FOLLOWING GROWTH HORMONE THERAPY IN GROWTH HORMONE (GH) DEFICIENT CHILDREN.

Lynne L. Levitsky, George H. Lambert, Dale A. Schoeller, Deborah V. Edidin, Pritzker Sch. of Med., Univ. of Chicago, Michael Reese Hosp., Dept. of Pediat. and Medicine; Chicago, USA

Significant changes in hepatic drug clearance occur in the transition from childhood to adulthood. These changes probably parallel the functional capacity of the hepatic cytochrome P-450 dependent mixed function oxidase (MFO) system. GH decreases hepatic MFO activity in animals and may act similarly in humans. Caffeine labelled with stable ^{13}C has been shown to be a substrate for the MFO system. Five GH deficient children underwent CBT, with collections of expired air for $^{13}CO_2$ enrichment analysis following ingestion of ^{13}C-caffeine (3 mg/Kg) before, and 4-5 weeks following GH 0.1 u/Kg S.C. t.i.w. All children showed a decrease in % $^{13}CO_2$ dose exhaled over 2 hours following GH administration:
Pre 9.1±1.5, Post 7.3±2.9 ($p < .05$, paired t-test)
The CBT is a safe effective technique for the measurement of the hepatic MFO system. N-demethylation of caffeine is decreased by GH therapy in GH deficient children. The capacity for N-demethylation is highest in prepubertal children. This may partially correlate with changing patterns of GH release.

30 ACUTE AND CHRONIC EFFECTS OF CLONIDINE ON GROWTH HORMONE AND GONADOTROPIN SECRETION IN ADOLESCENT BOYS.

Sleman A. Khoury, Sue E. Sauder, Paula M. Hale, Nancy J. Hopwood, Inese Z. Beitins, John C. Marshall, & Robert P. Kelch Univ of Mich, Depts of Med & Peds, Ann Arbor, USA.

Clonidine, a presumed α2 agonist, is a potent stimulus for GH in man and gonadotropins in rodents. To assess the acute and chronic effects of this drug on GH and gonadotropins in adolescents, we studied 4 boys in early to mid-puberty, sampling blood every 15-20 min for LH and FSH ($\bar{x}$ ± SE mIU/ml) and hourly for GH, before and after one or two oral 0.15mg/m² doses of clonidine. (*=p<.05 vs control):

Pt. #	CA/BA (yr)	Control Day LH	Control Day FSH	Control Night LH	Control Night FSH	Clonidine Day LH	Clonidine Day FSH	Clonidine Night LH	Clonidine Night FSH
1	17/14	1.5 ±0.1	1.1 ±0.1	4.4 ±0.3	1.7 ±0.1	2.3 ±0.2	1.4* ±0.1	5.7* ±0.3	2.5* ±0.1
2	15/13	2.9 ±0.1	0.7 ±0.1	4.1 ±0.2	0.5 ±0.1	3.5* ±0.1	0.5 ±0.1	4.7* ±0.2	1.0* ±0.1
3	14/14			2.5 ±0.1	1.2 ±0.2	2.5 ±0.1	0.9 ±0.1	3.0* ±0.1	1.0 ±0.1
4	13/13			5.2 ±0.5	5.1 ±0.4	1.7 ±0.2	4.9 0.5	5.6* ±0.3	6.2* 0.5
4R	(pt. #4 was restudied after 4mo of BID clonidine therapy for Tourrette Syndrome)							4.9 ±0.4	6.2 ±0.3

Clonidine had no effect on LH pulse frequency or the circadian pattern of LH, FSH or GH secretion. It was consistently followed within 2h by a GH peak comparable to the spontaneous pulses. This effect on GH was maintained in pt. #4 after chronic therapy. We conclude: 1) clonidine has a modest effect, if any, on gonadotropins at this stage of human puberty; 2) growth should be followed closely in adolescents on clonidine therapy.

31 GROWTH HORMONE SECRETORY PATTERNS - AID TO DIAGNOSIS OF GROWTH PROBLEMS.

Nancy J. Hopwood, George E. Bacon, Inese Z. Beitins, Paula M. Hale, Tarina M. Mendes, Robert P. Kelch, University of Michigan Medical Center, Department of Pediatrics, Ann Arbor, MI USA

Since GH responses to provocative (PGH) stimuli are often not reflective of physiological GH secretion, PGH was compared with integrated physiological GH secretion (ICGH) in 133 children and adolescents ages 4-18, with abnormal growth (<5th or >95th % for height and/or abnormal growth velocity). ICGH was determined by continuous ambulatory blood withdrawal pump (collected in one hr aliquots) over 12 h (1800-0600) or 24 h (1800-1800) in 87, or by 12 h intermittent q 20 min sampling (1800-0600) in 46 patients. The following morning all children had either arginine-insulin (AI) induced hypoglycemia (118) or oral clonidine (C) (15) tests. Serum somatomedin C, T/E_2, bone age and T_4 were also correlated with growth velocity and GH responses. In 33, 24 h ICGH correlated highly with, but was not more informative than 12 h ICGH (1800-0600) performed in all patients. Discordant GH levels (PGH vs ICGH, x and peaks) were present in 47 of 120 (40-50% of children with constitutional delay (CD) of growth), depending on the criteria for normality used. Low ICGH (<2 ng/ml) was seen in 42, and borderline ICGH (2-3 ng/ml) in 21. Low (<7 ng/ml) or borderline (7-10 mg/ml) GH responses to AI or C were seen in 48 and 19 children respectively. ICGH was useful in excluding a Dx of GH deficiency (GHD) in 14 patients with low PGH, while the Dx GHD was further substantiated in 26 patients. ICGH proved most valuable in patients with CD-delayed adolescence and/or emotional stress where "transient" GHD and discordant GH values are often obtained on pharmacologic testing.

32 LONGITUDINAL HEIGHT AND HEIGHT VELOCITY STANDARDS FOR NORTH AMERICAN CHILDREN: CHARTS ALLOWING FOR EARLY AND LATE MATURATION.

James M. Tanner and Peter S. W. Davies, University of London Institute of Child Health, Department of Growth and Development, London, U.K.

Height and height velocity centile charts have been developed for North American children. Though similar in form to the Tanner-Whitehouse-Takaishi charts for British children, they use colour printing to present more information than is in the British charts, specifically centiles for early and late maturing children for height attained as well as for height velocity. The amplitude of the centiles in pre-puberty and adulthood is based on the National Child Health Survey data and the shape of the velocity and tempo-conditional distance curves on American longitudinal growth data, supplemented with recent Swedish and Swiss longitudinal studies. We think they are the appropriate tool for clinicians in North America wishing to follow children through the pubertal period.