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Final results of long-term hGH treatment in 55 patients with idiopathic GH deficiency and 30 patients with craniopharyngioma.

This paper assesses the factors which contribute to the ultimate result, as regards adult stature and body proportions, of long-term hGH treatment. It concerns 39 patients with idiopathic isolated GH deficiency (GHD), 10 with idiopathic GH plus gonadotrophin deficiency (GnD), 6 with idiopathic multiple hormone deficiency (MPHD) and 30 with multiple deficiencies following craniopharyngiomas (CR). Treatment averaged 5½ years and terminated when growth ceased. Final height in isolated GHD averaged 2.3 SD below the population mean (untreated, about 6 SD). Half the boys, but only 15% of the girls ended above the 3rd centile. Pubertal development and the adolescent growth spurt were normal. The trunk/limb proportion was normal. Final height was more affected by mid-parent height (correlation 0.72) than by any other factor, but the degree of smallness at initial treatment also, independently, affected it (partial correlation 0.37). Age at initial treatment, duration of treatment and first year velocity were uncorrelated with final height. Patients with GHD plus GnD, with MPHD and with CR ended up taller (-1.5, -1.0, -1.2 SD) but entirely because their legs were (disproportionately) longer. Length of leg and body proportions depend on when sex steroids are begun. These results indicate that the unrecovered 2 SD of height in GHD was lost early in childhood, and emphasise the importance of early diagnosis, before the patient's height is too far below normal standards.

23 L. AKSNES* and D. AARSKOG. Department of Pediatrics, University of Bergen, Bergen, Norway. Serum levels of Vitamin D metabolites in puberty.

In order to relate the Vitamin D metabolism in puberty to sex, sexual maturation, and indirectly, to growth velocity and cessation, the serum levels of 25-OHD, 1.25-$(OH)_2D$, 24,25-$(OH)_2D$, 25,26-$(OH)_2D$ were measured in 177 normal adolescent girls and boys. The mean values of 25-OHD, 24,25-$(OH)_2D$, and 25,26-$(OH)_2D$ showed seasonal variation with significantly higher levels in early autumn than late spring. There were significant correlations between the levels of 25-OHD and 24,25-$(OH)_2D$ ($r=0.85$, $p<0.0005$) and 25,26-$(OH)_2D$($r=0.49$,$p<0.0005$). In girls 1.25-$(OH)_2D$ increased from age 11 to a peak at 12 ($p<0.0005$) and then decreased. In boys the rise occurred between age 13 to 14 ($p<0.0005$) with subsequent decline. At ages 12 and 13 years girls had significantly higher levels than boys ($p<0.0025$). When the 1.25-$(OH)_2D$ values were related to stage of puberty, the girls showed maximal increase between stages 1 and 2 ($p<0.0005$) with a peak at stage 3, whereas the boys showed a significant increase from stage 2 to a peak at stage 3 ($p<0.01$). In both sexes there were subsequent significantly decreasing values to stages 4 through 5. The ratio of 24,25-$(OH)_2D$ to 25-OHD varied inversely with the 1.25-$(OH)_2D$ concentration with lowest value at age 12 in both sexes, followed by a gradual increase to a plateau at age 15 in the girls and 17 in the boys. Vitamin D is required for normal bone formation, and the changes in Vitamin D metabolism presumably reflect increased demands at puberty.

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Growth Hormone Causes a Rise in 1,25-diOH D and Sensitizes the Kidney to Parathormone.

GH replacement therapy (Rx) causes rapid skeletal growth, some suggest by GH-dependent 25-OH D 1-hydroxylase activation. We studied 12 GH deficient children before and for 1 wk after high dose (5IU/da) Rx, and at 1 mo, 3 mo and 1 y after conventional (0.1 IU/kg x 3/wk) Rx. Unstimulated (Uns) ionized calcium (Ca) did not change. Likewise, Uns PTH (1-84, N<57µlEq/ml) did not vary from 38.9 ± 2.6 before Rx (all are mean ± SEM). 24-h urinary cyclic AMP excretion corrected for volume of glomerular filtrate (GF) (UcAMP) did not change within 1 wk (2.99 ± 0.20 nmole/dl GF, 3.15 ± 0.24 after), but had risen by 3 mo to 4.51 ± 0.70 ($p<0.05$) and by 1 y to 6.64 ± 1.50 ($p<0.02$). Uns calcitonin (CT) (1-32, N<107 pg/ml) fell from 29.4 ± 2.8 before to 21.5 ± 1.8 after ($p< 0.05$), but was not different from preRx by 1 y (43.4 ± 11.0). In 6 of the children, 1,25-diOH D rose from 31.1 ± 1.9 pg/ml to 45.8 ± 4.0 ($p<0.001$) during the first week following inception. By 1 mo, 1,25-diOH D had fallen to 43.0 ± 7.1 ($p<0.02$) and by 3 mo was no longer different from basal. In summary 1) GH Rx induced a rapid rise in 1,25-diOH D, which fell again by 3 mo. 2) Uns CT fell immediately after Rx, but was no different from initial by 1 y. 3) Although Uns Ca and PTH did not vary, 4) UcAMP rose progressively. Conclusion: GH activates the 1-hydroxylase during early Rx and sensitizes the kidney to parathormone by 3 mo.

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Biological Effect of Estradiol on phosphatase activities in rabbit cultured chondrocytes. Clinica Infantil, Barcelona, Spain, and Hôpital des Enfants Malades, Paris, France.

Estrogens stimulate skeletal growth in human during puberty but increase cartilage maturation. Between all the metabolic transformations which occur during maturation of growth plate cartilage, there is an increase in alcaline phosphatase in the precalcified zone. In this study, chondrocytes in culture were prepared from male or female rabbits of different ages. The cells deprived of foetal calf serum for 20 hours were then incubated with increasing concentrations (10^{-12}M to 10^{-7}M) of estradiol during 24 hours. Alcaline and acid phosphatase activities were then measured using paranitrophenylphosphate as substrate. In chondrocytes from female rabbits one can observe an increase in phosphatase activities between 10^{-11}M to 10^{-9}M. At lower and higher concentrations, the phosphatase activities remain as control. This stimulation is present, whatever the age of the rabbit (300g, 1000g, 2000g). No effect is observed when chondrocytes from 300g male rabbits are used. A slight but significant inhibition of phosphatase activities is shown using chondrocytes from 1000g or 2000g male rabbits.

In conclusion, estradiol stimulates acid and alcaline phosphatase activities in cartilage in vitro. This effect is sex dependent but does not seem to be related to the age of the animal.

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Primary hyperparathyroidism (PHP) in infancy associated with familial hypocalciuric hypercalcemia (HcHc).

PHP is rare in infants. A girl with hypotonia, constipation and poor feeding from birth had markedly elevated serum concentrations of total Ca (3.33-3.59 mmol/l), free Ca (1.47-1.45 mmol/l) and PTH (1.44-1.40 ug/l); s-Ph (1.27-1.32 mmol/l) was low, and urinary excretion of Ca and Ph was normal. Treatment with Ca-restricted diet, prednison, calcitonin, phosphate and furosemid was not succesful, and a partial parathyroidectomy was performed at the age of 12 months. Histological examination showed "light-chief-cell" type. Following surgery, total s-Ca (2.98-3.04 mmol/l) and free s-Ca (1.59 mmol/l) and s-PTH (0.78-0.80 ug/l) concentration decreased, but remained above normal level.

A family study (n=30) revealed HcHc in the mother, sister and in 3 other relatives suggesting an autosomal dominant inheritance. The total s-Ca (2.87-3.05 mmol/l) and free s-Ca (1.50-1.53 mmol/l) were increased, s-Ph (0.9-1.05 mmol/l) and s-PTH concentrations were normal; urinary Ca and Ph excretions were low. These individuals have no symptoms of hypercalcemia. Urinary concentration of cyclic AMP was normal in the index patient as well as in the other family members. These diagnostic and therapeutical implications have to be considered.

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Impaired response to acute phosphorus (P) deprivation in familial hypophosphatemic rickets (HR).

While reduced renal tubular P reabsorption is regarded as the primary abnormality in HR, the mechanism(s) are not understood. The existence of a defect in 1,25 dihydroxyvitamin D (1,25$(OH)_2D$) generation in HR remains controversial. Dietary P deprivation (PD) is the most potent stimulus to P reabsorption and induces 1,25$(OH)_2D$ formation. Therefore, we used PD to test the integrity of renal P conservation and 1,25$(OH)_2D$ generation in HR. 5 untreated men with HR and 5 male controls (C) were placed on a 500 mg P diet with 24 g $Al_2(OH)_3$/day for 4 days. During PD HR excreted twice as much P/day as controls and showed a much smaller rise in P reabsorption (TmP/GFR).

	Controls		HR	
	Baseline	PD	Baseline	PD
serum P(mg/dl)	3.0±.3	2.6±.3	1.9±.1	1.7±.1
urine P(mg/24 hr)	1032±87	90.8±44	1150±75	181±71
TmP/GFR(mg/dl)	2.7±.3	3.8±.3	1.8±.1	2.2±.1
1,25$(OH)_2D$(pg/ml)	52±2	68±5	43±6	33±6
urine cAMP(nmol/dlGF)	2.42±2	2.73±.3	4.11±.5	3.1±.2

PD induced a rise in 1,25$(OH)_2D$ in C ($p<.05$) while levels fell in HR. The ucAMP data suggest that the defect in P conservation in HR is not PTH mediated. The paradoxical 1,25$(OH)_2D$ response to PD, paralleling that seen in hyp mice confirms that 1,25$(OH)_2D$ generation is abnormal in HR.