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DISTINCT SEXUAL DIMORPHISM IN THE EFFECT OF HYPOTHYROIDISM (HYP) ON GROWTH HORMONE RECEPTOR (GHR) & GH-BINDING PROTEIN (GHBP) GENE TRANSCRIPTION IN THE RAT.

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While the role of thyroid hormones(TH) in the transcriptional regulation of a wide variety of genes is well documented, its role in the regulation of the GHR and GH-binding protein (GHBP) gene is not known. To study the effect of HYP on the transcription of the GHR & GHBP gene, we induced HYP by thyroidectomy in male(HYP/♂) and female(HYP/♀) rats (n=6 each group) and four wks later compared them to age and sex matched euthyroid control rats. Compared to the control group, the HYP rats had decreased T4 (mean ± SD, 7.0 ± 1.4 vs 2.3 ± 0.8 µg/dl, p <0.01) and increased TSH (63 ± 3 vs 3 ± 0.5 ng/ml, p<0.01). After extraction of total RNA, steady state levels of mRNA for GHR & GHBP in liver were measured by northern analysis and ribonuclease protection assay. Whereas levels of hepatic GHR & GHBP mRNA were decreased (p <0.01) in HYP/♂ rats, levels of hepatic GHR & GHBP mRNA were increased (p <0.01) in HYP/♀ rats when each group was compared to its appropriate controls. These differences could not be attributed to differences in circulating levels of GH (9.8 ± 2.7 vs 13.4 ± 13.1 ng/ml , HYP/♀ vs HYP/♂). We conclude that (1) TH affects the transcription of GHR & GHBP genes, and (2) there is distinct sexual dimorhpism in the effect of HYP on GHR/GHBP gene transcription.

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CAN COST EFFECTIVENESS OF GROWTH HORMONE BE IMPROVED?

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We report the growth velocities of all growth hormone-deficient, *pre-pubertal* patients treated since onset of therapy with a daily dose of recombinant hGH in our clinic. As illustrated in the table below, our patients attained adequate growth velocities while treated with approximately 60% of the dose most widely used. The study population consisted of 20 pre-pubertal patients, 9 of whom had "organic" and 11 of whom had idiopathic etiologies of their growth hormone deficiency. Average age at onset of treatment was 6.6 years. Average bone age maturation during treatment was 1.2 years for each year of chronological age. The growth velocities in the second and third year of treatment did not decline from those of the first year. Of note, Ranke and Guilbaud (*Acta Paedtr. Scand* [Suppl] 379: 109-115,1991) have found that high first year doses of hGH have a negative influence on second year growth. Since both cost and metabolic side effects increase with the magnitude of the hGH dose, current recommended dosages may need to be reviewed.

Yr. hGH	Study hGH dose (mg/kg/wk)	Study Hgt. vel. (cm/yr)
1	0.177	7.7
2	0.175	8.8
3	0.171	9

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GROWTH AND FINAL HEIGHT (Ht) AFTER TREATMENT (Rx) FOR HODGKIN'S DISEASE (HD)

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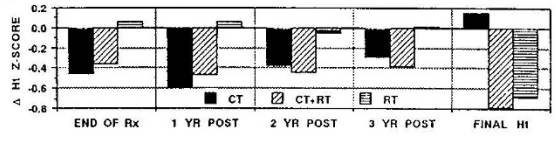
We evaluated growth in 49 children (34 males) diagnosed with HD at mean age of 8.4 yrs (2.4-11.8 yrs). Pts were treated with: radiation (RT) only, 13 pts; chemotherapy (CT) only, 8 pts; combination CT+RT, 29 pts. CT consisted of Cyclophosphamide, Adriamycin, Vincristine, Procarbazine and Prednisone. Mean RT dose was 30 Gy (0.2-51). Six of 41 irradiated pts received total lymphoid irradiation (TLI), 21 mantle, and 14 only involved field. Ht was obtained at diagnosis, at end of Rx (0.5 yr for RT only, 1-1.5 yrs for CT±RT), 1, 2, 3 yrs post-Rx, and at attainment of final ht. The mean change (Δ) in ht z-score for CT, CT+RT, and RT are, respectively: -0.45, -0.36, 0.06 at end of Rx; -0.60, -0.46, 0.06 1 yr post-Rx; -0.37, -0.44, -0.05 2 yr post-Rx; -0.29, -0.38, 0.01 3 yr post-Rx; 0.15 (2 Pts), -0.79 (16 Pts), -0.68 (6 Pts) final ht (fig). Ht decreased significantly at end of Rx for CT (p=0.008) and CT+RT (p=0.0002) but not for RT alone (p=0.26). There was a trend for continued reduction in ht z-score between end of Rx and final ht for RT and CT+RT. Change in ht z-score did not correlate with age at diagnosis, sex, or stage of disease. We conclude that children Rx'ed for HD with CT±RT experience a modest but significant loss in ht z-score, that appears to be permanent in those Rx'ed with CT+RT.



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EFFECTS OF GROWTH HORMONE THERAPY IN GROWTH HORMONE DEFICIENT AND SHORT NON-DEFICIENT CHILDREN.

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We evaluated the change of predicted final adult height and height standard deviation scores for chronological age (CA) and bone age (BA) after two years of therapy with standard doses of biosynthetic growth hormone. Thirty-four growth hormone deficient children (25 boys, 9 girls) and thirty-four short, slowly growing, non-deficient children (25 boys, 9 girls) were followed longitudinally while on treatment. Height, weight, BA, and CA were recorded just before and at the completion of two years of growth hormone treatment. Using these, the pre and post-treatment predicted adult height (PAH), height standard deviation scores based on CA (ZCA) and on BA (ZBA) were derived. ZCA and ZBA were calculated from Tanner and Davies (J. Pediatr, 1985,107:317). PAH were calculated by the method of Roche, Wainer, and Thissen. Mean CA (years) at the initiation of treatment, in the deficient group, was 11.7±3.5 for boys and 10.5±3.2 for girls while mean BA was 9.2±3.6 for boys and 8.7±3 for girls. Mean CA was 11.7±2.1 and 10.5±2.3 while mean BA was 9.7±2.2 and 8.36±2.1 for boys and girls respectively, in the non-deficient group. Changes in PAH were not correlated with pre-treatment BA. Changes in Z-score and PAH were as shown in the table (* denotes p<0.05 vs. pre-treatment).

	GH Status	ZCA		ZBA		PAH (cm)	
		Pre-Rx	On Rx	Pre-Rx	On Rx	Pre-Rx	On Rx
BOYS	Def	-3.3±0.8	-2.0±0.8*	-1.0±1.0	-0.3±0.9*	162.0±6.6	167.8±8.5*
	Non-def	-2.7±0.6	-2.3±0.6*	-1.0±0.9	-0.5±0.6*	165.8±5.0	170.3±3.8*
GIRLS	Def	-3.4±1.5	-2.4±1.2*	-1.9±0.6	-1.3±1.1	151.7±10.9	155.0±9.6*
	Non-def	-2.6±0.7	-2.0±0.8*	-0.9±0.8	-1.2±1.1	157.7±3.4	158.4±6.7

Deficient and non deficient children of both sexes improved in their ZCA but only boys improved significantly in ZBA. Only the non-deficient girls failed to show improvement in their PAH. **Conclusion:** These preliminary data suggest that 2 years of growth hormone therapy has a beneficial effect on PAH and ZBA in boys irrespective of growth hormone status but that the benefit to non-deficient girls, if any, is slight. More advanced skeletal maturity did not appear to have an adverse effect on the PAH response to therapy. Follow-up to final height is needed to determine the ultimate validity of treatment-associated improvements in ZBA and in PAH as calculated by the RWT method.

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THE EFFECT OF GROWTH HORMONE (GH) AND IGF-I ON CLONOGENIC GROWTH OF HEMATOPOIETIC CELLS IN LEUKEMIC PATIENTS DURING ACTIVE DISEASE AND DURING REMISSION.

The number of survivors of childhood leukemia treated with GH for growth failure is increasing. The debate around the direct or indirect relationship of GH and IGF-I to the occurrence or recurrence of malignancy, especially in the case of GH therapy in patients with leukemia, is still unresolved. After we have studied the effect of GH and IGF-I on bone marrow (BM) of patients with acute leukemia (ALL and AML) in active disease, we studied patients with chronic myelogenous leukemia (CML) in remission. We have shown that GH increases blast colony count (BCC) by a mean of 68% and 77% at a GH concentrations of 250 and 300 ng/ml respectively. IGF-I increased BCC in ALL patients by 50, 93 and 105% at IGF-I concentrations of 0.05, 0.25 and 0.5 ng/ml respectively and in AML patients by 33, 58 and 65% in the presence of same concentrations. In 3 CML patients in remission a granulocyte-macrophage colony forming assay did not reveal stimulation of peripheral blood blast colony forming by GH or IGF-I. In contrast with our in vitro data (as previously reported by us) that suggest that GH and IGF-I may promote blast cell proliferation, this effect was not seen on cells obtained from leukemia patients in remission.

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CULTURED HUMAN FETAL CHONDROCYTES (HFC) TO ASSESS THE BIOLOGICAL ACTIVITY OF HORMONES INVOLVED IN THE GROWTH PROCESS.

Growth hormone (GH) 200 ng/ml, IGF-I 50 ng/ml and dehydrotestosterone (DHT) 10 microMol effects on proli-feration, proteoglycan (PG) synthesis, IGF-I and GH binding protein (GH-BP) production of cultured HFC (7-12 weeks old) was studied. Single cell suspension was obtained by trypsinization (1% for 45 min.) concomita-ntly with mechanical homogenization. 1-2*10^6 cells/ml were seeded and grown for 7 days when confluence occurred, as well as piles of cells and cartilage noduli. At 7 days a subculture in DCCM-1 w/o serum was used used to test the response to exogenous hormones. Chondrogenic nature of cells was confirmed by histochem-ical staining, detection of cartilaginous markers by immuno histochemistry for collagen type II and aggrican In case of a limited supply of cells HFC were grown in droplets of hydrated gel (alginic acid beads). The proliferative effect of cells was 65% to GH, 50% to IGF-I and 35% to DHT. Typical dose response curves were obtained with these hormones. While endogenous IGF-I was detected in culture no change in GH-BP levels was noted. Autocrine paracrine response to GH and DHT in FHC is suggested.