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**77** LHRH ANALOG ADMINISTRATION TO PUBERTAL CHILDREN WITH ISOLATED GH DEFICIENCY.

In children with isolated GH deficiency, not treated early with hGH, final height may be compromised by puberty initiation. Previous attempts to inhibit pubertal development in such subjects by cyproterone acetate failed to improve final height. We attempted to inhibit puberty with LHRH analog in two adolescents with isolated GH deficiency, aged 14.5 years (case I) and 12 years (case II) respectively, in order to prolong the growth period and possibly improve final height. One received LHRH analog by nasal spray and the other IM monthly injection (TRp<sup>6</sup> microcapsule). hGH was given IM, 4IU 3 times weekly. The most pertinent data are listed below:

	case I (nasal)	case II (IM)
Duration of Rx (months)	15	32
Δ height (cm)	6	14
Δ bone age (months)	4	12
Testes (ml) before/after	15/9	15/9
LH peak (mIU/ml) post LHRH/after	3.8	3.4
Testosterone ng/dl before/after	300/40	280/70

Although it is too early to predict the efficacy of such intervention, a ratio of Δht. age to ΔB.age greater than 2 suggests that improvement in final height might be achieved. This however requires confirmation by longer follow-up period.

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 EFFECT OF GROWTH HORMONE (GH) ANTIBODIES ON THE GH CONCENTRATIONS OBTAINED AFTER ADMINISTRATION OF BIOSYNTHETIC GH TO CHILDREN

Little is known of the effect of GH antibodies (GHABS) on the bioavailability of administered GH. We have developed methods for measuring free GH concentrations (FGH), using a polyethylene glycol (PEG) extraction, and total GH concentrations (TGH), by acid dissociation of the GH-GHABS complex followed by PEG precipitation of antibody. Standard plasma GH concentrations (PGH) were measured by immunoradiometric assay.

Correlation coefficient of 0.98 were found between FGH, TGH and PGH in 24 hour profiles from tall children.

GHABS have been observed in 48% of 427 children treated with various preparations of biosynthetic GH. TGH, FGH and PGH concentrations were measured in samples from 126 of these children. In 31 who had developed GHABS, TGH and PGH concentrations were markedly elevated compared to FGH concentrations. In the remaining children without GHABS, there were no differences.

GH profiles were obtained over 12-24 hours after injection of GH from 5 children who developed GHABS which were significantly different from the profiles observed in 5 children without GHABS. The GH peak was observed at 6 rather than at 3 hours and circulating GH was detectable 12-18 hours following administration compared to 8-10 hours. These alterations did not affect the growth response to therapy but could have implications for the development of sustained release preparations.

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**79**

A RADIOIMMUNOPRECIPITATION ASSAY (RIPA) FOR ANTIBODIES TO GROWTH HORMONE (GH)

A highly sensitive radioimmunoprecipitation assay for antibodies to growth hormone was developed for monitoring children treated with currently available 22K methionyl and natural sequence GH preparations. Serum (50 µl) was incubated for 24 h with 125-Iodine-labelled 22K natural sequence GH (76 µCi/µg, 20,000 cpm per tube) in buffer (200 µl): 0.04 mol/l sodium phosphate and 0.1 mol/l sodium chloride, pH 7.4. Antibody-bound GH was precipitated with polyethylene glycol 150 g/l. The distribution of binding by control sera was skewed and was normalized by log transformation. Binding of >5.2% was considered positive [99% confidence]. Specificity of binding was confirmed by incubation with unlabelled GH. Four hundred and twenty-seven children were screened: 81 were controls, 346 had been treated with GH for 3 months or more. In patients treated with pituitary and methionyl GH, 13/77 had antibodies (median binding; range) (6.9; 5.4 - 24.6%); with pituitary GH 35/40 (7.3; 5.4 - 27.2%); with natural sequence GH 6/67 (15.1; 6.7 - 25.0%), and with methionyl GH only 71/162 (23.1; 5.7 - 57.1%) Of children who had received cranio-spinal irradiation 10/33 had very high titres (45.7; 28.3 - 57.1%), suggesting an altered immunological response in this group.

We have validated a specific and sensitive RIPA for the detection of GH antibodies in serum.

**80**

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 MODULATING EFFECT OF GROWTH HORMONE (GH) ON "IN VITRO" LYMPHOPROLIFERATION (LP).

In order to investigate the ability of GH and GH-releasing hormone (GH-RH) to modulate LP "in vitro", peripheral blood lymphocytes (PBL) from healthy adults were stimulated with PHA in the presence of increasing concentrations of biosynthetic GH (Somatonorm) (0.425x10<sup>3</sup>-501.5x10<sup>3</sup> ng/ml) and of GH-RH (1-29, Kabi-Vitrum) (0.006-50 µg/ml). The results obtained show that low doses of GH and GH-RH increase LP "in vitro", while high concentrations of the hormones (GH:8.5x10<sup>3</sup> ng/ml; GH-RH:0.048 µg/ml) induce a progressive decrease of PHA-induced LP. No differences in cell viability were observed with and without GH and GH-RH and comparable percentages of TAC<sup>+</sup> cells and of IL-2 production were found in all conditions tested. Nevertheless, when exogenous recombinant IL-2 was added to PHA-induced PBL culture with high doses of GH or GH-RH, a reconstitution of LP was observed. Further experiments seem to exclude the presence of T-suppressor lymphocyte induction by GH and GH-RH. The present results suggest the hypothesis that high doses of GH and GH-RH may interfere with the binding between IL-2 and its membrane receptor on activated lymphocytes.

**81**

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 INFLUENCE OF BIOSYNTHETIC GROWTH HORMONE (GH) THERAPY ON THE IMMUNE SYSTEM OF GH-DEFICIENT CHILDREN.

The ability of GH to influence humoral and cell-mediated immunity was evaluated in 21 GH-deficient children, 1.3-17.7 yr, before and during therapy with biosynthetic GH (Somatonorm) (12U/mq) injected three times weekly. Blood was collected prior to GH treatment (Gr. A), then following the 1<sup>st</sup> week (Gr. B), then again at the 3<sup>rd</sup>-6<sup>th</sup> month (Gr. C), and finally at the 9<sup>th</sup>-12<sup>th</sup> month of therapy. Cell-mediated immunity was assessed by quantitation of T lymphocyte subpopulations (T total, helper and suppressor cells) using monoclonal antibodies (OKT3, OKT4, OKT8). No variations in serum immunoglobulin levels were observed throughout treatment period. Pretreatment OKT3, OKT4, OKT8 values (Gr. A) were within the normal range and did not change after the 1<sup>st</sup> week of GH therapy (Gr. B). However, following 3-6 month GH treatment (Gr. C), OKT3 significantly increased (70.61±1.84 vs 78.38±1.14, p<0.001), OKT4 decreased (46.71±1.81 vs 40.23±2.09, p<0.01), OKT8 increased (25.00±1.44 vs 34.09±1.71, p<0.001) and OKT4/OKT8 ratios decreased (2.01±0.16 vs 1.34±0.10, p<0.001). At the 9<sup>th</sup>-12<sup>th</sup> month of therapy (Gr. D), the percentage of T cells was not significantly different from pretreatment values. Our data suggest some relationship between GH and thymic-dependent immune function.

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**82**

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GROWTH HORMONE TREATMENT IN CHILDREN AFTER CRANIAL IRRADIATION.

Growth response to treatment with GH 0,1 IU/kg s.c.x7 (Crescormon later changed to Somatonorm) was evaluated in 9 prepubertal children who had received cranial irradiation mean 4 years before when treated for a cranial tumor (braintumor, retinoblastoma or rhabdomyosarcoma of the epipharynx). The children were totally GH-deficient or with subnormal GH-secretion based on provocative tests. All had a markedly disturbed 24-h-GH-profile. No other hormonal deficits were present at the start of GH-treatment. During the first year on GH-treatment a catch up in growth velocity was seen with an increment from mean 3 cm/year to 8,5 cm/year (mean -2,2 SDS to +3,5 SDS). During the second year growth velocity decreased somewhat but still remained at an increased speed corresponding to +1,9 SDS. The actual mean height of the children increased from -1,6 SD to -0,4 SD after two years treatment. The increment in growth in these children corresponds well with that seen in partially GH-deficient children of other etiology and is somewhat less than catch up growth seen in totally GH-deficient children. Our results are however better than previously reported for irradiated children. This might be due to the higher dose and frequency of GH-administration in this study.