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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 (TRP⁶ 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 inter-
vention, 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 (GHAES) 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.

GHAES 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
GHAES, TGH and PGH concentrations were markedly elevated compared to FGH
concentrations. In the remaining children without GHAES, there were no
differences.

GH profiles were obtained over 12-24 hours after injection of GH from 5
children who developed GHAES which were significantly different from the
profiles observed in 5 children without GHAES. 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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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.

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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 hor-
mone (GH-RH) to modulate LP "in vitro", peripheral blood lymphocy-
tes (PBL) from healthy adults were stimulated with PHA in the pre-
sence of increasing concentrations of biosynthetic GH (Somatorm) (0.425×10^{-3} - 501.5×10^{-3} 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 hor-
mones (GH: 8.5×10^{-3} 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⁺ 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 reconsti-
tution 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 membra-
ne receptor on activated lymphocytes.

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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 immu-
nity was evaluated in 21 GH-deficient children, 1.3-17.7 yr, befo-
re and during therapy with biosynthetic GH (Somatorm) (12U/mq) im
injected three times weekly. Blood was collected prior to GH
treatment (Gr. A), then following the 1st week (Gr. B), then again
at the 3rd - 6th month (Gr. C), and finally at the 9th - 12th 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 varia-
tions in serum immunoglobulin levels were observed through treat-
ment period. Pretreatment OKT3, OKT4, OKT8 values (Gr. A) were
within the normal range and did not change after the 1st 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 ra-
tios decreased (2.01 ± 0.16 vs 1.34 ± 0.10 , $p < 0.001$). At the 9th - 12th
month of therapy (Gr. D), the percentage of T cells was not signi-
ficantly different from pretreatment values. Our data suggest some
relationship between GH and thymic-dependent immune function.

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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 Somatorm) 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 velo-
city 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 treat-
ment. 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-de-
ficient 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.