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IMMUNOLOGICAL CHANGES TO GROWTH HORMONE THERAPY IN GROWTH HORMONE DEFICIENCY.

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In order to determine the role of growth hormone (GH) on immunological functions, several kinds of lymphocyte subsets and killer cell activities including natural killer (NK), interferone-augmented NK, and lymphokine activated killer (LAK) celles were studied in 12 children and 12 adults with GH deficiency. The results were compared with age-matched normal controls. Adult patients had been previously treated with hGH in childhood. In child patients, NK and LAK activities were significantly low before hGH therapy, but they increased to normal levels after one year of hGH therapy. However, a significant low percentage of Leu 7^+ cells was observed both before and after hGH therapy in 11 children. In adult patients, NK activities were normal, but interferon-augmented NK activities and LAK activities were low. However, LAK activities increased after one month of hGH therapy. These results suggest that in children GH deficiency may cause the defective killer cell activities, and that hGH therapy may recover the function of killer cells, though the number of killer cells remained at a low level. In adult patients, short term hGH therapy resulted in normalization of LAK activities but did not resulted in normalization of other cellular immunological abnormalities. Therefore, GH is thought to be indispensable to develop and maintain some killer cell activities.

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IGFs AND IGF BINDING PROTEINS IN HUMAN CORD SERA: RELATIONSHIP TO INTRAUTEINE GROWTH

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The IGF autocrine/paracrine system is believed to play a major role in the regulation of human fetal growth. We have examined the ontogeny of IGF-I,IGF-II,IGFBP-1,2,3 concentrations in fetal development throughout gestation using cord sera from 97 normal newborns between 26 and 42 weeks. We also compared these variables with those from 18 SFD and 9 LFD newboms.

IGF-I and IGF-II were measured by RIA and ELISA after acid-ethanol extraction. IGFBP-1,2,3 were measured by ELISA newly deveoloped.

In relation to gestational age and birth weight, IGF-I and IGFBP-3 had positive correlation and IGFBP-1 had negative correlation. IGF-II and IGFBP-2 did not show any correlation. In cord sera from SFD newborns the decreased IGF-I and IGFBP-3 levels and the increased IGFBP-1 levels were observed. In contrast, in LFD cord sera these variables were not significantly different from those of normals.

These results imply that these IGF-related peptides play significant role in human fetal growth by positive and negative regulatory mechanism. In contrast IGF-II and IGFBP-2 do not play a role in fetal growth during late stage of fetal development.

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GROWTH OF PUBERTAL SHORT NORMAL CHILDREN TREATED 3 YEARS WITH GROWTH HORMONE ALONE OR ASSOCIATED WITH LHRH AGONIST J.C. Job and F.Landier, Hopital St Vincent, Paris, and Kabi Pharmacia, France.

30 adolescents starting puberty with a short height and slow growth without detected cause were treated 3 yrs with GH 0.1U/kg/day and randomized in group A (GH alone) or B (GH+ D-Trp6-LHRH 3.7 mg/mnth the first 2 years).Among them were 14 F (8A,6B) age 10.5-14.5 yrs, stage P2B2 (8)or B3 (6), uterine length 41 ±4mm and bone age (BA) 10.5±0.7 years); and 16 M (7A,9B) age 12.5-15.5 yrs, 7 P2 and 9 P3, plasma testosterone 2.10 ±0.93 ng/ml, BA 12.6 ±0.8 yrs. Puberty was suppressed for 2 yrs in group B.No side-effects occurred.Compliance was good the first 2 yrs. 2 M(1A,1B) and 3 F(A) stopped before end of year 3. Results (Height SD/age, Growth velocity, Height age/Bone Age ratio, and Bayley-Pinneau's Predictable Height) were:

Height M(A)0yr:-2.5(.6),3yrs:-1.5(.4);(B)0yr:-2.9(.6),3yrs:-2.6(.9)
F(A)0yr:-2.7(.6),3yrs:-1.6(.8);(B)0yr:-2.8(.5),3yrs:-2.1(.9)

GV cm/yr:M(A)0yr 3.2(2.1),1yr 9.7(1.0);(B)0yr 4.1(1.6),1yr 5.9(0.9)
F(A)0yr 4.2(0.7),1yr 8.1(1.2);(B)0yr 3.8(1.2),1yr 6.6(1.4)

HA/BA: M(A)0yr .90(.05),3yrs .95(.04);(B)0yr .88(.04),3yrs .94(.04)
F(A)0yr .88(.10),3yrs .90(.12);(B)0yr .93(.17),3yrs .91(.12)

PH cm: M(A)0yr 164(5.7),3yrs 169(2.2);(B)0yr 165(4.2),3yrs 167(4.1)
F(A)0yr 148(8.3),3yrs 153(6.8);(B)0yr 150(9.2),3yrs 154(8.3)

Except for GV increase in gr.A on 1st year, no results within each group nor differences from A to B were significant. Preventing sex development for 2 yrs had no advantage. Final results, with BA near to closure, showed good improvement of HA/BA and gain of 5 to 10 cm of PH in 12/30 sujects:6A(3M,3F) and 6B(3M,3F). Factors possibly involved in the differences of individual results will be discussed

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SERUM IGF-1 AND IGFBP-1 LEVELS IN INFANTS WITH CONGENITAL HEART DISEASE. JS Barton, A Harris, PC Hindmarsh and MA Preece, International Growth Research Centre, Institute of Child Health, London, WC1N 1EH, UK.

Severe congenital heart disease (CHD) is frequently associated with early growth failure. We have investigated growth and nutritional status prospectively in 62 infants with CHD and in 40 healthy, age-matched controls. Measurements of serum IGF-1 and IGFBP-1, which are both considered useful nutritional markers, have been measured by specific RIA after a 4 hour fast, at the time of cardiac catheterisation or surgery and have been related to growth and dietary intake data estimated from 3-day records. At a median age of 0.98 (range 0.02-2.70) years growth failure was evident.

Mean Length SDS	-0.96	95% CI (-1.27 to -0.66)
Mean Weight SDS	-1.96	95% CI (-2.29 to -1.64)
Mean Body Mass Index SDS	-1.84	95% CI (-2.17 to -1.51)

Serum IGF-1 was significantly lower in infants with CHD than in controls (mean IGF-1 for CHD = 30 ng/ml v 61 ng/ml in controls; P<0.001). Within the study group serum IGF-1 was weakly correlated with weight (r=0.34) and calorie intake (r=0.33) but no combination of variables studied explained more than 10% of the variance in serum IGF-1. A BMI SDS <-2.0 was associated with significantly lower IGF-1 levels (mean IGF-1 = 23 ng/ml v 38 ng/ml in those with BMI SDS >-2.0; P=0.03). IGF-1 levels were similar in patients with and without cyanosis. IGFBP-1 was inversely correlated with age (r=-0.43) but was not correlated with any anthropometric parameter studied. Mean serum IGFBP-1 was 441 (95%CI 370-525) ng/ml in those <1 year (Normal 69 ng/ml; non-fasting*) and 292 (250-341) ng/ml in older subjects (Normal 55 ng/ml; non-fasting*). The low IGF-1 and elevated IGFBP-1 levels suggest that nutritional deficiency is an important factor in the poor growth seen in CHD.

(*Hall et al., Acta Endocrinol (1988), 118: 321-326)

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EFFECT OF A CONTINUOUS INFUSION OF A SOMATOSTATIN ANALOGUE ON GROWTH RATE, GROWTH HORMONE SECRETION AND HEIGHT PREDICTION IN TALL CHILDREN

We studied the effects of reducing growth hormone (GH) secretion on the growth rate and change in height prediction of 9 tall children (5 F;4M). All children had height predictions of 180cms or more and received a continuous infusion of a somatostatin analogue (Octreotide) (SMS) in a dose of between 50 and 100 micrograms given over a 12 hour period for 1 year. SMS infusion significantly reducted mean 24 hr GH concentrations after 7 days of administration (mean GH pre SMS 5.3 mU/l; mean GH at 1 week 2.2 mU/l). This reduction was maintained over the year of treatment ($p < 0.01$). SMS treatment increased the percentage of time during the 24 hr period at which serum GH concentrations were lower than the sensitivity of the assay (mean increment over 1 year 27%). Serum insulin like growth factor 1 concentrations remained unchanged during the course of treatment. Growth rate over the year of treatment was reduced by between 30 and 40%. A significant reduction in height prediction of 4cms resulted from SMS treatment for one year (P=0.03). No adverse effect on thyroid status or parameters of glucose metabolism were observed. These data suggest that SMS treatment may play an important role in reducing growth rate, height prediction and ultimately final height in children with tall stature. The specific effect of SMS on the GH axis suggest that this treatment may be of value in the prepubertal tall child.

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CLINICAL APPLICATION OF AN ELUTED STAIN ASSAY FOR THE MEASUREMENT OF GH BIOACTIVITY

We have applied the Eluted Stain Assay (ESTA) system to the bioassay of growth hormone. The assay is based upon reduction of the yellow tetrazolium salt MTT to its purple formazan by lactogen-activated Nb2 rat lymphoma cells. The assay is precise and sensitive (detection limit 0.04 mU/L). Adaptation of the assay for the measurement of GH in patient sera was achieved by the use of a monoclonal anti-serum to prolactin and by dilution of patient serum to 0.625% or less to resolve complex serum effects. **We aimed to** compare bioactive and immunoactive GH concentrations in various clinical settings. We observed a greater increase in the bioactivity of GH when compared with an immunoassay (Hybritech IRMA) after intravenous administration of different doses of GHRH (0.005mg GHRH: increase in ESTA GH concentration 46mU/l compared with 17.5mU/L by IRMA; 0.05mg GHRH: increase in ESTA GH 30mU/L compared with 12.4mU/L by IRMA). Peak GH concentrations in response to intravenous insulin (0.15U/kg) also read differently (peak GH ESTA 119.9±5.9; IRMA 59.5mU/L). This discrepancy between bioactive and immunoactive GH concentrations was less pronounced with spontaneous GH peaks (GH ESTA 37.2±0.7; GH Hybritech 29.3 mU/L). Oxandrolone, a growth-promoting agent had minimal effect on bioactive:immunoactive (B:I) GH ratios in children with constitutional delay of growth and puberty (B:I ratio pre-oxandrolone 1.0; B:I on oxandrolone 1.2). **We conclude that** subtle changes in the bio:immunoactivity of GH released in response to GHRH and insulin can be demonstrated in the ESTA bioassay. These changes may be of relevance in the interpretation of GH provocation tests.