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Catch-up growth after changing from 3 times weekly i.m. to daily s.c. injection of human growth hormone (HGH) monitored by knemometry in HGH deficient children.

It is now possible to study short-term growth by knemometry, a non-invasive technique measuring the exact distance between heel and knee in sitting children. During the measurement the lower leg length (LLL) is determined by repeatedly moving the child's knee under the measuring board. Each single measurement consists of six independent estimations, the SD of which is <0.1 mm. In 14 HGH deficient patients we saw a significant ($P < 0.01$) elongation of LLL 24 hrs after single injections of 4 IU HGH i.m. This increase, although lasting for about 24 hrs only, was 0.47 ± 0.10(SE) mm and exceeded the mean daily LLL growth of 6 healthy children (0.07 ± 0.10 mm) by the factor 7. Since daily s.c. injections of HGH are more physiological than alternating i.m. doses, we compared LLL growth rates after transfer from 3 times weekly i.m. to daily s.c. administration of HGH (same weekly dose) in 7 HGH deficient patients, age 5 - 20 yrs. All had been treated with HGH for 6 months to 7 yrs before the study. While LLL growth rates ranged from -0.015 mm/day (no growth) to 0.07 mm/d during i.m. treatment, they were significantly higher (0.047 to 0.084 mm/d) in all patients 30 - 127 days after changing to daily s.c. treatment. In conclusion, daily s.c. application of HGH induces catch-up growth after transfer from alternating i.m. administration and thus seems to be the preferable regimen.

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Glucose production in hypopituitary children.

Hypopituitarism in infancy is associated with hypoglycemia, which has been attributed to enhanced utilization of glucose because of decreased availability of FFA and ketones. To test this hypothesis, we measured glucose kinetics in seven hypopituitary infants, using a 2-hour continuous tracing infusion of D-[6,6-H_2^2] glucose after 6-12 hour fasting. During the study blood glucose decreased from 76 ± 13 (SD) to 58 ± 13 mg/dl, the consequence of a glucose production (2.8 ± 1.2 mg/kg^{-1}/mn^{-1}) decreased to 62% of normal. Plasma lactate (927 ± 771 µM) and alanine (317 ± 298 µM) were normal. FFA (760 ± 210 µM) and 3-hydroxybutyrate (369 ± 311 µM) were lower than in fasting controls.

Conclusions: (1) In infancy, pituitary hormones are necessary to maintain an adequate glucose production during fasting. (2) The decrease of glucose production in hypopituitary infants is unrelated to reduced gluconeogenic substrates. (3) Despite decreased lipid substrates, fasted hypopituitary infants have a low level of glucose utilization.

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An improved radioreceptor assay for human growth hormone using an HPLC-purified ^{125}I-hGH.

Human growth hormone (hGH) was labelled with ^{125}Iodine to a specific activity of 50-80 µCi/µg by a stoichiometric modification of the chloramine-T method. After labelling, the crude reaction mixture containing ^{125}I-hGH, unreacted iodide, chloramine-T, salts, etc. was purified by reverse-phase high performance liquid chromatography (HPLC) using a Synchropak RP-P column (Altech, USA) and a linear gradient. Biological activity of the purified material was measured by binding to IM-9 lymphocyte hGH receptors. The results were compared with those obtained after purification by gel filtration using a sephadex G-100 column. HPLC gave a much better separation than sephadex chromatography. The improved resolution was the result of an increase both in selectivity and efficiency. The analysis time was considerably reduced by HPLC (30 min vs 5 h). The recovery was comparable in both methods (95 %). Specific binding of ^{125}I-hGH to lymphocyte membrane receptors was higher by 20 % with the preparation purified by HPLC than with the sephadex material. The maximum bindability of the hormone by an excess of lymphocyte receptors was 86 % for the HPLC-purified ^{125}I-hGH and 71 % for the sephadex-purified ^{125}I-hGH. Both preparations behaved similarly in kinetic experiments. It is concluded that HPLC is a fast, convenient and reproducible method for purifying ^{125}I-hGH for receptor studies.

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Estrogens promote growth: Experimental and clinical evidence.

Although increasing estradiol levels accompany the pubertal growth spurt in girls our understanding of the effects of estrogens on growth has been dominated by the experience with high doses in tall girls. - In male Wistar rats castrated on age day 27 and treated with ethinylestradiol (EE) (250-25-2.5-1-0.25 µg/kg BW d s.c.) until age day 45 the three highest doses showed to be inhibiting body growth, GH, SM and gonadotropins. The lowest dose however enhanced body growth. The effects on bone maturity were inversely related to dose. In girls with multiple pituitary hormone deficiencies (MPHD) treated with low doses of EE (5µg/d p.o.) corresponding observations were made. In 5 patients (CA: $\bar{x}$=18.0 yrs.; BA: $\bar{x}$=12.3 yrs) treated for 6-12 mo. with EE (-and constance of other medication-) height velocity increased from $\bar{x}$=3.4 to 4.5 cm/yr. without unduely advancing BA, but inducing signs of puberty. Preliminary observations suggest positive effects on growth with EE doses suboptimal in respect to the induction of the female sex characteristics.

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Somatostatin decrease associated with growth hormone increase after TRH injection in constitutionally tall adolescents.

12 adolescents referred for excessive height prediction were studied. Somatostatin like immunoreactivity (SLI) and plasma GH levels were measured during saline infusion and after TRH injection. SLI was measured after extraction by RIA with antibody against 14 cyclic somatostatin. In 6 subjects, TRH induced a sharp increase of GH from 2.3 ± 0.6 ng/ml to 23 ± 3.6 ng/ml; SLI dropped by 60% averaging 12.1 ± 5.8 pg/ml before and 4.8 ± 4.1 pg/ml during the 20 to 60 min after TRH injection. In 6 other patients TRH induced no significant changes of plasma GH (3.1 ± 1.1 ng/ml) nor SLI (11.3 ± 4.1 pg/ml). During the saline infusion mean levels of SLI were the same in the 2 groups of subjects (12 ± 4.8 pg/ml). 5 GH responders subjects undergone bromocriptine treatment (5 mg/day). After 3 months of this treatment the paradoxical rise of GH and the drop in SLI levels after TRH injection were suppressed. It is thus hypothesized that the GH release after TRH in tall adolescents is due to a decrease inhibitory effect of somatostatin at the pituitary level.

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Treatment of male and female precocious puberty (PP) by monthly injections of a continuous release preparation of D-Trp-6-LH-RH.

Successful treatment of PP by daily subcutaneous (SC) administration of the LH-RH agonist D-Trp-6-LH-RH (Trp6) was reported (Kauli et al., ESPE 1983). After demonstration of its efficiency and innocuity in dogs, a long acting preparation designed for releasing continuously 100 µg Trp6 per 24 h, was given intramuscularly to 3 boys and 3 girls with PP, aged 3 to 8 years. 3 mg Trp6 were injected every 28 days, cyproterone acetate being associated during the first week. In boys testosterone levels (ng/ml) decreased from 2.2-5 to 0.1-0.2 within 2 months. Testis volume was unaffected in 1, decreased slighty in 2. In girls estradiol levels (pg/ml) decreased from 40-100 to 0-40 within 2 months and in a menstruating girl genital bleeding desappeared after 1 month. Breast enlargement was reduced in all. In all children, the gonadotropin responses to LH-RH were suppressed and the inhibition of gonadal secretion persisted after 6 months of treatment. The data demonstrate the ability of long acting Trp6 to suppress gonadal secretion by a monthly injection in children with PP.