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GROWTH HORMONE (GH) DIRECTLY ENHANCES CHONDROGENESIS  
AND OSTEOGENESIS IN VITRO.

To study the direct effect of GH on chondrogenesis and osteogenesis 2 model systems were used. An organ culture of newborn mice mandibular condyle were maintained on collagenous sponge, cemented onto stainless steel mesh for 6 days. The addition of 50 ng/ml recombinant human GH (hGH) caused within 3 days a marked enlargement of the proliferative zone from  $56 \pm 6$  to  $120 \pm 11$  microns. The width of the chondroblast layer increased by hGH from  $66 \pm 9$  to  $199 \pm 7$  microns, reflecting significant proliferation, and that of the chondrocytic layer from  $288 \pm 22$  to  $465 \pm 9$  microns, reflecting differentiation. The calcified cartilage shrank from  $400 \pm 12$  to  $333 \pm 29$  microns. In a separate tissue culture system of mice chondroprogenitor cells, the undifferentiated cells developed within 3 days to a cartilage nodule which by 6 days grew further. The addition of 50 ng/ml hGH to the medium produced a marked increase in the nodule size from  $20 \pm 2$  to  $46 \pm 6$  and from  $76 \pm 7$  to  $380 \pm 12$  mm<sup>2</sup> on days 3 and 6 resp. The perichondrium width increased from  $100 \pm 12$  to  $149 \pm 7$  microns on day 6, and that of the cartilage layer from  $242 \pm 10$  to  $477 \pm 12$  microns. Moreover, under hGH we observed the appearance of calcified cartilage and osteogenesis of bone trabecules, osteocytes, osteoblasts and osteoclasts, which were absent in the absence of hGH. We conclude that hGH has a direct effect on chondrogenesis and osteogenesis in tissue and organ culture, which are both proliferative and differentiative.

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### FACTORS CONTRIBUTING TO IMPAIRMENT OF GROWTH IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

In 88 ALL pat. (43 ♂; 45 ♀) studied retrospectively, mean chronological age (CA) at diagnosis was 6.0 yrs,

mean SDS of height for CA (+0.40SD), height for bone age (BA) (+0.44 SD) and weight (-0.06SD). In 48 pat. now in puberty, mean height for CA has decreased to -0.73SD and mean height for BA is -1.71SD. In 8 pat. final height is -0.68SD when adult height predicted at diagnosis was +0.32SD. Growth impairment was determined by the following: 1) duration of chemotherapy: 5 yrs after diagnosis, mean height SDS for CA was reduced by -0.65 SD and by -1.01 SD respectively in patients treated for 2 and for 5 yrs. 2) Radiation doses: 5 yrs after diagnosis mean height SDS for CA was reduced by -0.34 SD and by -1.14 SD in those receiving 18 Gy and 24 Gy respectively. 3) Lack of catch-up growth after therapy: between end of therapy and onset of puberty, height SDS for CA did not change (-0.06 SD). In 16/33 euthyroid pat. evaluated at least 2 yrs after irradiation GH response was blunted ( $< 10$  ng/ml) in 2 pharmacological tests. In 11/30 Sm-C was low for CA. No hGH treatment was given. 4) Early puberty in relation to age at diagnosis: in girls diagnosed before or after age 7, M<sub>2</sub> started respectively at mean CA of 10.6 yrs (n=16) and 11.4 (n=15), accounting for a difference of -0.4 SD in height for CA at puberty. 5) Reduction of pubertal growth spurt: compared to average normal girls, mean pubertal height gain was reduced by 3.8 cm. Pituitary-gonadal function (GnRH-test, n=30) was normal. Conclusion: In ALL pat. growth impairment has several components, differing by time of occurrence and mechanism.

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### BLUNTED PUBERTAL GROWTH AFTER LEUKEMIA: A NEW PATTERN OF GH-INSUFFICIENCY

Growth and age at menarche were studied in 10 girls previously treated for Acute lymphoblastic leukemia, ALL. These girls had normal prepubertal growth after treatment but a subnormal pubertal growth spurt. Their mean final height was 1 SD less than expected before puberty. The average age at menarche was 12.2 years which is significantly lower ( $p < 0.01$ ) than the normal mean for Swedish girls, 13.1 years.

Spontaneous secretion of Growth hormone, GH, was studied during 24 hours in thirteen girls, 2.9-7.3 years after the ending of therapy. Blood samples were taken every 30 minutes and the results were compared with the secretion of normal children. The mean 24-hour secretion for these girls was severely blunted and there was no increase in the secretion during puberty.

We suggest that girls who have been treated for ALL, including CNS-irradiation, have a form of relative GH-insufficiency previously not described. This insufficiency becomes clinically obvious only when the girls cannot respond to the increased demands for GH during puberty.

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### PRECOCIOUS OR EARLY PUBERTY AND GROWTH FAILURE IN GIRLS TREATED FOR ACUTE LYMPHOBLASTIC LEUKAEMIA.

We have studied 31 girls with ALL who have been treated with prophylactic 1800 - 2400 cGy to the cranial meninges; 3 girls had further cranial irradiation following relapse. All had been treated with intrathecal Methotrexate in addition to systemic chemotherapy. Mean age of onset of puberty was 8.4 yrs (range 6.7 - 10.0); 5 had precocious puberty. Early puberty as a sequelae of prophylactic low-dose cranial irradiation occurred predominantly in girls, which is compatible with our hypothesis for the mechanism of the timing of the onset of sexual maturation.

21 girls had an absent or inadequate growth acceleration of puberty. Pharmacological tests of GH secretion were unreliable at diagnosing GH insufficiency, not least because standards for GH secretion in normal puberty were not available. Early or precocious puberty combined with GH insufficiency may produce severe growth failure and we have used a treatment regimen of either intranasal (D-Ser<sup>6</sup>) GnRH or Depot (D-Trp<sup>6</sup>) GnRH in combination with biosynthetic Met-GH. We have been able to compare the treatment of 10 girls treated by this combined regimen for up to 1.5 yrs with 19 girls who had no endocrine therapy. The rate of advancement of epiphyseal maturation slowed and growth rate increased during treatment, although longer treatment periods will be required to assess the affect on final height.