In one set of studies, we have evaluated the role of endogenous TGF-β responsiveness in the maintenance of the differentiated phenotype of myoblasts and osteoblasts. We therefore abrogated the responsiveness to TGF-β in established osteoblasts and myoblasts that can differentiate into myoutubes in culture. Our results indicate an important role of continuous TGF-β responsiveness in these well-differentiated cell types. In other studies we focussed on the biological activities of vgr-1/BMP-6, a TGF-β family member which is specifically expressed in hypertrophic cartilage, but for which no functional information is as yet available. Transfected CHO cells overexpressing murine vgr-1/BMP-6 were derived and recombinant vgr-1/BMP-6 was purified to serve as a source of the factor thus allowing us to evaluate its role in osteogenesis and chondrogenesis in culture. In addition, transfected CHO cells overexpressing vgr-1/BMP-6 were inoculated into mice and the effect of vgr-1/BMP-6 on the phenotype of the resulting tumors was evaluated by histological analysis. Studies of this type should allow us to define the natural role of the different TGF-β family members in the mesenchymal differentiation pathways.

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EFFECTS OF 17βESTRADIOL ON HUMAN CARTILAGE CELL PROLIFERATION AND DIFFERENTIATION..O. Blanchard, L. Tsagris and M.T.Corvol, INSERM U30, Hopital Enfants Malades, Paris, 75015, France.

Surgical biopsies from 27 girls and 18 boys aged between 2 and 8 years were used to prepare high density primary cultures of chondrocytes in serum-free culture medium. The children were considered normal in term of skeletal growth. Cell multiplication and collagen type II biosynthesis and secretion by the cultured cells were studied in the absence or in the presence of 10^{-10}M 17β estradiol or testosterone. Chondrocyte multiplication, performed in the presence of 10ng/ml of bFGF, was never modified by the addition of sex steroid hormones. By contrast, when estradiol or testosterone were added to the cells at confluency, a significant increased of type II collagen peptide was recovered in the treated cells as compared with non treated ones. Cycloheximide (10^{-7}M) did not completely inhibit the increased amount of type II collagen peptide recovered in hormone treated cells. At the mRNA level, as evaluated by northen blot analysis, the steroids induced only a two fold increase of type II collagen transcripts. The stimulating effect of 17β estradiol was always higher than the one of testosterone. A possible effect of testosterone through its metabolic conversion into estrogens was suggested, since the cultured chondrocytes appeared to contain aromatase activities. No significant increase of chondrocyte collagen content was observed when the steroid hormones were added during the division phase of the culture. Interleukine 1 (IL1) which is known to stimulate the collagenase secretion by chondrocytes, was added at the concentration of 50ng/ml, to confluent chondrocytes cultured from two prepubertal girls. A significant decrease of chondrocyte collagen type II was found and was not observed in the presence of 17β estradiol added at 10^{-9}M during three days. These data suggest that sex steroid hormones are acting on the differentiation more than the proliferation of chondrocytes. Sex steroid hormones may maintain cartilage cell phenotype by modulating both the synthesis and the degradation of chondrocyte specific proteins.

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BONE MASS GROWTH DURING NORMAL PUBERTAL DEVELOPMENT. G.E. Theintz, B. Buchs, R. Rizzoli, D. Slosman, H. Clavien, P.C. Sizonenko and J.Ph. Bonjour. Divisions of Biology of Growth & Reproduction, Clinical Pathophysiology and Nuclear Medicine, University Hospital, Geneva, Switzerland.

Bone mineral density (BMD, gr/cm²) and content (BMC, gr) were determined at the levels of the lumbar vertebrae (L2-L4), femoral neck (FN) and midfemoral shaft (FS) using DEX absorptiometry at 1-yr interval in 198 healthy adolescents (98 females, 100 males) aged 9-19 yrs. BMD/ BMC values were related to age, height, weight, pubertal stage and to environmental variables such as calcium intake and the level of physical activity. In females, the gain in BMD/BMC was sustained from 11 to 14 yrs but fell dramatically after 16 yrs and/ or 2 yrs after menarche. In males, the BMD/ BMC gain was elevated from 13 to 17 yrs and then declined markedly, remaining significant between 17 and 20 yrs for L2-L4 BMD/BMC and FS BMD only. Large interindividual variations were observed between height increments and bone mass gain with a relationship evolving according to a loop pattern. Multiple regression analysis showed that weight was the strongest predictor of bone mass at each site. Nutrition and exercise improved the R^2 of the overall model by only 6% at L2-L4 and 4.1% at FN. Their effect on FS was negligible (+0.7%). During the normal pubertal development of average subjects, the effects of environmental factors appear to be outweighed by the large gain of bone mass due to puberty itself. These effects should therefore be easier to demonstrate in prepubertal children: this point appears of relevance for future intervention programmes aiming at maximizing bone mass gain during growth.

Final Height Symposium

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FINAL HEIGHT ATTAINMENT IN NORMAL CHILDREN WITH SHORT STATURE TREATED WITH GROWTH HORMONE. International Task Force (ITF) Report, H. Guyda, Division of Endocrinology and Metabolism, Montreal Children's Hospital, Montreal, Canada.

The mandate of the ITF was defined in order to determine the outcome in terms of final height attainment in short normal children of normal birth weight who have been treated continuously with GH for at least three years. After considerable discussion, the ITF developed a questionnaire for this purpose, which was provided to all investigators who had indicated by preliminary survey that they had data that could be made available for analysis. Several significant issues were recognized that would make data collection and analysis difficult. These included the limited number of children who have attained final height, the influence of puberty onset occurring during GH therapy, the enormously variable protocols that have been employed with both pituitary-extracted and biosynthetic growth hormone, the absence of a suitable control group that would span the genetic heterogeneity of the study populations, and the interruption of therapy in some children as a result of the CJD crisis in 1985. Data analysis will include initial bone age (BA) and mid-parental height to assess genetic potential, one-year pre-treatment growth velocity (GV) to determine height SDS at onset, height attained at two years after initiation of continuous therapy, and final height attained after at least a total of three years of GH therapy (BA fused and/or GV < 2 cm/yr.). Historical controls will be developed from untreated normal short stature children who have reached adult height by analysis of databases in several countries, including Germany, Sweden, and Denmark. A comparative analysis will also be made of those children with the diagnosis of GHD that have been treated with GH and attained final height, but who retest as 'normal' following discontinuation of GH therapy. It is anticipated that this task force will be able to provide at least a preliminary final height outcome statement in regard to short children who have received growth hormone for a significant period of their childhood. It will also recommend that a similar analysis be conducted in the future in regard to psychological and educational outcome variables in these children.

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HEIGHT DEVELOPMENT IN TURNER SYNDROME (TS): RESULTS OF AN INTERNATIONAL SURVEY CONDUCTED BY ESPE/LWPES. M.B.Ranke for the ESPE/LWPES, Section for Paed. Endocr., Univ. Children's Hospital, D-7400 Tuebingen, Germany.

Recent attempts to improve height in TS through growth hormone therapy have stimulated worldwide interest in the spontaneous growth and final height of these patients. Published data show that women with TS reach a mean height of approx. 20 cm. below the normal female population, even if the karyotypes differed. TS-specific age-related growth curves, however, show distinct variability, particularly during childhood. This is probably due to the bias introduced by the circumstances leading to the diagnosis, e.g. pre-natal diagnosis through karyotyping, early diagnosis through dysmorphology and/or organ abnormalities, diagnosis during childhood following persistent short stature, delayed or absence of puberty, or infertility in adult life. Thus, data on adult height, drawn from patients whose diagnosis was made very late, cannot govern the height prognostics used for patients who are recognized much earlier. Height prognosis in TS, therefore, needs to be further individualized by taking parental height, karyotype, size at birth, degree of dysmorphology, bone age and ethnically-representative growth curves into consideration. Current data supports the view that GH therapy can improve both height in childhood and in adult life in TS.

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A PREDICTION MODEL FOR THE FIRST YEAR GROWTH RESPONSE TO GROWTH HORMONE IN TURNER SYNDROME (TS) BASED ON KIGS (Kabi Pharmacia International Growth Study) DATA. M.B. Ranke*, O. Guilbaud, A. Price, A. Wallström for the KIGS International Board. *Section for Paed. Endocrinol., Univ. Children's Hospital, D-7400 Tuebingen, Germany.

In order to optimize treatment with GH, a large-scale, complex analysis on the response to GH in terms of auxological data, as well as treatment modalities is essential.[1] We analyzed 175 TS patients <11 yrs. The median values were: CA=7.9 yrs; HT SDS=-2.5 SD; target HT=0.0 SD; Weight for Height index (WHI %)=97; GH dose (IU/kg/wk)=0.8; No. of GH inj/wk=6). Out of 10 potential predictors, only the following were validated: No. of inj/wk, GH dose, CA and WHI. The corresponding regression equation is: HV (cm/yr)=9.02 + [0.36 x No. inj/wk] + [2.01 x GH dose (IU/kg/wk)] - [0.25 x CA (yrs)] - [0.036 x WHI (%)]; r2=0.37; error SD=1.26 cm/yr). We concluded firstly that the mode of treatment rather than the auxology determines growth in TS, early treatment being possibly advantageous. Secondly, in contrast to GHD, WHI is negatively correlated to the growth response, thus pointing to a different body composition in TS. Thirdly, we found the growth response to GH in TS was less predictable with the variables used. Lastly, other predictors eg. degree of dysmorphology, may improve the prediction model.

[1] *Acta Paediatr Scand (Suppl) 370:122-130, 1990*