11 M. KLAGSBRUN*, R. LANGER* and C. LILLEHEI* (Intr. by H.K.A. Visser). Stimulation of DNA Synthesis in Cultured Fibroblasts and Chondrocytes by a Cartilage-Derived Growth Factor. Children's Hospital Medical Center and Harvard Medical School, Boston, Mass. 02115.

A growth factor derived from bovine cartilage is described which stimulates DNA synthesis and cell division in cultured fibroblasts and chondrocytes. This growth factor is obtained by extraction of bovine scapular cartilage from 1-14 day old calves with 1M guanidine hydrochloride. Further purification is achieved by ion exchange chromatography using a cationic ion exchange resin. The active fraction is eluted with 0.02M ammonium acetate, pH 8.5. This fraction stimulates DNA synthesis in mouse Balb/c-3T3 cells and NIH/3T3 cells. It also stimulates DNA synthesis in confluent, resting chondrocytes cultured from scapular cartilage of adult New Zealand white rabbits. The growth factor is inactivated by trypsin. On gel filtration in 4M guanidine hydrochloride the growth factor chromatographs in the region of cytochrome c, indicating a molecular weight of 12,000-13,000 daltons. The occurrence of both growth factor and chondrocytes in the same tissue suggests a possible physiological role for this factor in the regulation of cartilage growth.

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Serum somatomedin (SM) and cartilage metabolism in malnourished and refed rats.

SM and inhibitors were estimated by the porcine bioassay in acutely fasted, marasmic (M) and marasmic-kwashiorkor (MK) rats. In vitro endogenous activity and responsiveness to SM was measured in their costal cartilage using S35-sulfate and H3-thymidine. Acute fasting for 3-4 days resulted in complete loss of SM activity, partly caused by a heat-labile, non-dialysable inhibitor. Cartilage endogenous activity and responsiveness were depressed. M-rats (paired with MK, normal food, + 4 g/day, from 25 days age) after 1, 2 and 5 weeks had SM potency ratios compared to controls of 0.8, 0, 0.15, with diminished cartilage endogenous activity. MK rats (ad lib. isocaloric 0.5% casein food) showed a profounder depression of growth and cartilage endogenous activity despite SM ratios (to controls) of 0.34, 0.75 and 0.45 after 1, 2 and 5 weeks. Evidence for a circulating inhibitor was found. On refeeding M rats, SM and cartilage responsiveness increased by 24 hrs and cartilage endogenous activity by 48 hrs. However catch-up growth in length seen after 1 and 2 weeks was best reflected by H3-thymidine uptake. Clearly differences in SM activity and target organ metabolism follow different nutritional insults. Further studies of these models may clarify the relative roles of SM and inhibitors in malnutrition.

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Somatomedin Activity in Growth Disorders.

Somatomedin activity (SMA) has been measured using an embryonic chick cartilage assay in normal and short normal children, children with retarded growth due to pituitary GH deficiency and children with accelerated growth due to sexual precocity. Samples were taken fasting between 09.00 and 10.00 hours. Pooled adult serum was used as reference standard. The following results were obtained: normal and short normal (n = 29) 1.06 ± 0.27 , GH deficiency (n = 20) 0.81 ± 0.19 ($p < 0.001$), sexual precocity (n = 11) 1.27 ± 0.22 ($p < 0.02$). In all groups a highly significant correlation with bone age ($r = 0.78$) has been demonstrated. The acute short term effect of HGH administration on SMA in 12 children has also been studied to obtain a predictive index of growth response. A significant response was not seen in any children within 48 hours following HGH 10 mgs I.M. A response did occur at 3 and 6 hours following a second injection in 6 children.

16 L. DAVID*, B. BETEND*, P. CHOPARD* and G. TEYSSIER* (intr. by R. Francois) Service de Pédiatrie, S bis, Hôpital Edouard Herriot and Unité INSERM U 34, Lyon, France.
Further evidence for a feed-back loop between parathyroid hormone (PTH) and vitamin D (vit D) metabolites: acute decrease of serum immunoreactive PTH (iPTH) in normocalcemic vitamin D deficient rickets (vit D.D.R.) after vitamin D₂ load.

The secondary hyperparathyroidism (HPT) present in normocalcemic vit D.D.R. is not clearly understood. Recent studies indicating that a feed-back loop may be present between PTH and 1,25 dihydroxycholecalciferol, we have examined the acute effect of a vit D load on serum iPTH levels in 5 infants (age 5 to 11 months) with normocalcemic vit D.D.R. They all presented a clinical history compatible with vit D deficiency and marked typical bone lesions of rickets. Serum Ca ranged from 8.9 to 9.6 mg/100ml, serum P from 3.8 to 5.5 mg/100ml and serum alkaline phosphatase (A.Pase) from 84 to 225 iu(N50). Elevated serum iPTH levels were present: 280 to 670 pEq/ml(N<100). A unique oral vit D₂ load (600 000 u) was given. In all infants a marked decrease in serum iPTH was observed 24 and 48 h later (serum iPTH at 48 h: 115 to 360 pEq/ml - Δ iPTH: 140 to 450 pEq/ml) with no consistent changes in serum Ca, P and A.Pase. Normal levels of serum iPTH were found on a control 10 to 18 days later, though serum A.Pase remained elevated and healing of bone lesions was incomplete. These results suggest that the HPT of normocalcemic vit D.D.R. is, at least in part, directly secondary to the lack of active metabolites of vit D, probably 1,25 dihydroxy vit D; they are also consistent with the concept of a feed-back loop between PTH and vitamin D metabolites.

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The effect of hyperparathyroidism on tubular reabsorption of amino acids in vitamin D resistant rickets (VDRR)

The tubular reabsorption of amino acids was investigated in 15 children with VDRR before treatment, following an acute injection of PTH, and after development of secondary hyperparathyroidism induced by continuous oral phosphate substitution. Before treatment 5 of 6 children had normal serum values of iPTH (22.5 U/ml). None of 15 patients showed a generalized defect in amino acid reabsorption, however tubular reabsorption of glycine was significantly reduced in 10 patients ($\%T\text{-gly} = 90.7\%$ vs. 96.5% in normals). After an acute i.v. application of 200 IU PTH there was no change in reabsorption of total amino acids ($\%T\text{-AA} = 98.0\%$) nor in glycine ($\%T\text{-gly} = 91.0\%$). Under treatment with oral phosphate and vitamin D 5 out of 10 children developed secondary hyperparathyroidism within 12 months (iPTH = 100.7 U/mL) while 5 patients had normal values (iPTH = 12.4 U/mL). In both groups the $\%T\text{-AA}$ (97.6% and 98.4% resp.) and $\%T\text{-gly}$ (91.3% and 92.3% resp.) were unchanged compared to the values before treatment. The results indicate, that acute and chronic hyperparathyroidism is not followed by hyperaminoaciduria in VDRR, as is postulated in vitamin D deficiency rickets.

18 H.P. KIND*, J. FISCHER*, P.P. RICKHAM*, B. STEINMANN*, H.P. GNEHM*, R. NÜSSL* and A. PRADER, Dept. of Pediatrics and Orthopedics, University of Zurich, Switzerland.
HYPERPARATHYROIDISM AND ALCAPTONURIA IN A NEONATE.

A.A., born at term, weight 3350 g, was the first child of healthy and related Turkish parents. He was admitted for investigation of "black urine". Homogentisinic acid was identified and alcaptonuria thus proven. In addition, he showed severe bone changes compatible with hyperparathyroidism. This diagnosis was corroborated by: progressive hypercalcemia (up to 15.5 mg%), low serum Pi (2.6 to 4.5 mg%), concomitant increase of alk. P'ase (85-168 IU) and of aminoaciduria, and high immunoreactive parathyroid hormone (iPTH, 900 ng/ml, normal < 40 ng/ml). After low calcium diet, withdrawal of daily vit. D₃ supplement (400 IU) and under hydrocortisone vit. D deficiency rickets developed: serum Ca fell to 7.7 mg%, Pi to 1.9 mg%, alk. P'ase rose to 240 IU, hyperaminoaciduria increased, iPTH was 283 ng/ml. Vit. D₃ therapy, 1000 IU/day, a dose normally sufficient to restore normocalcemia and to heal vit. D deficiency rickets, led to a relapse of hypercalcemia (serum Ca 13.6 mg%) within 4 days. Four parathyroid glands with histologically diffuse hyperplasia were removed. Within 1 day, serum iPTH and Ca dropped and hyperaminoaciduria disappeared. Alcaptonuria persisted. Postoperative hypoparathyroidism was treated with 1,25(OH)₂D₃ (1 µg/day) and calcium supplement, and normocalcemia was achieved. The course of the disease will be reported and the biochemical findings be discussed.