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136 Ultrastructural analysis of growth zone architecture.A SEM study in rats.

In the present study the architecture of the growth zone and its disturbance in various forms of metabolic bone disease were investigated.Epipyhses and metaphyses of rats were separated transversely by fracture or sectioned longitudinally.The specimens were prepared by critical point drying or (for the study of mineralized structures) by digestion with sodium hypochlorite.A stable functional system of epipyhseal bone plate growth cartilage and metaphyseal trabeculae is formed in a light weight construction by various collagen fiber systems, cell columns and a framework of calcified cartilage matrix.Individual cell columns are joined with the epipyhses by being inserted into holes of the lower surface of the epiphyseal bone plate.The columns are stabilized by a shroud like system of collagen fibers and connected with one another by other interchanging fiber systems.Other fibers run longitudinally into the metaphyseal bone.In the zone of calcification mineralized globules can be found within longitudinal and transverse septa, whereas the matrix plane in contact with the chondrocyte cell surface shows only a fine granular surface.It can be shown that metabollically induced disturbance of longitudinal growth (rickets, uremia) will distroy this functional system.

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137 Histochemical, ultrastructural and microchemical studies on growth cartilage in chondrodysplasias.

Histochemical, ultrastructural and microchemical studies were performed on small growth cartilage biopsies from 21 chondrodysplastics and 4 children with normal growth. The biopsies were carried out during orthopaedic surgery with the informed consent of the parents. The cartilage was separated from bone by microdissection of freeze-dried sections. Proteoglycans and collagen were extracted, purified and subjected to gel electrophoresis. CNBr collagen peptides were also analyzed in several cases. In Kniest disease the chondrocytes contain metachromatic inclusions. The ultrastructural study discloses large dilatations of the rough endoplasmic reticulum with a fibrillo-granular content. The gel electrophoresis of proteoglycans shows an abnormal supplementary band. In pseudo-achondroplasia the chondrocytes contain large vacuoles bound by rough endoplasmic reticulum with alternately electron-dense and lucent layers. The inclusions are positive for proteins and for tryptophan and resistant to collagenase. The gel electrophoretic pattern of proteoglycans is abnormal. In pycnodysostosis single smooth membrane bound inclusions with granular and lamellar structure are present in chondrocytes. The histochemical studies suggest a phospholipid content. The ultrastructural study of polyepiphyseal dysplasia discloses two distinct forms. In diastrophic dwarfism many cells of the basal zone are degenerated and the capsules have an abnormal organization. The data strongly suggest that the pathophysiology of certain chondrodysplasias is related to proteoglycan and lipid troubles of chondrocytes.

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XY females with camptomelic dwarfism - lack of male gonadal differentiation coupled with abnormal cartilage

Camptomelic dwarfism (CD) is a syndrome of multiple characteristic skeletal malformations (including angulated tibiae), dwarfism, tracheomalacia, muscular hypotonia and early death. Both familial and sporadic occurrence have been described. There is a majority of fenotypically female individuals among the cases reported (20/25), although CD may occur in both sexes. Two cases of CD are presented, both with male karyotype but female fenotype. One died at 4 days of age, one at 11 months. Lab data at 1 month: LH 1.56 mIU/ml, FSH 16.2 mIU/ml, testosterone 0.05 ng/ml. Blood chemistry normal. At autopsy normal female genitalia were found. Microscopical examination of the ovaries revealed ovarian stroma containing tubules similar to the rete ovarii found in normal newborn girls, and occasional germ cells. Epiphyseal cartilage was structurally and biochemically abnormal; impaired growth of the cartilage but normal mineralization, and abnormal ratio of chondroitin-4-sulphate and -6-sulphate in the presence of high concentrations of collagen. The lack of testicular development might be explained by a lack of a "testis organizing factor" (H-Y-antigen?). In future, this easily recognized malformation syndrome should focus interest on the gonadal function and structure in these children, to test this hypothesis.

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Bone mass in thalassemic children.

Bone mass has been studied very little in b-thalassemic patients By making duplicate measurements of cortical thickness on the metacarpus of both hands, it is possible to calculate the cortical thickness in each child with an error of less than 5%. Our material consists of 50 thalassemic children treated regularly by transfusions and 20 controls aged 5-15 years. We found that the cortical thickness in thalassemic children was smaller than in the controls. The bone loss was more obvious in girls ($p<0.0005$) than in boys ($p<0.05$). The pretranfusion mean value for blood Hb was during the 12 months before the estimation of cortical thickness 7.26±0.9 g/100ml for girls and 7.3±0.5g/100ml for boys. A comparison in the thalassemic children between males and females showed that the cortical thickness was smaller in females than in males ($0.1>p>0.05$). The greater bone loss in girls than in boys could not be explained by the level of blood Hb because in both groups the mean value was the same. Of the 12 thalassemic children observed for 9-24months, 9 showed no significant bone change, 2 an improvement of cortical thickness and only one bone loss. Of the 10 thalassemic children observed for 25-48 months,4 showed a significant bone loss and 6 no change of the bone mass. In both groups the mean value of pretransfusion blood Hb was 7.4g/100ml and the sex distribution equal. This finding may mean that the bone loss in this age group of thalassemic children needs more than 24months to be obvious radiologically when the pretransfusion blood Hb is 7-8g/100ml.

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Epidemiology of inherited disorders of calcium/phosphate metabolism

In the years 1973 to 1975 a systematic screening for clinically recognisable disorders of calcium/phosphate metabolism was carried out among 55,000 children, 0-14 years of age. Besides, serum alkaline phosphatase activity was determined in an unselected sample of 1070 children, and urinary calcium output was measured in 529 subjects. Detailed family investigation was performed in each of the positive cases.

As a result of this programme 19 anomalies were discovered: 2 vitamin D-resistant hypophosphataemic rickets, 5 vitamin D-dependent rickets, 2 juvenile hypophosphatasia, 3 idiopathic hypercalcaemia, 7 idiopathic hypercalciuria. Considering only the index patients of the affected families, the following minimum estimate figures of prevalence could be calculated:

vitamin D-resistant rickets	1/27,500
vitamin D-dependent rickets	1/11,000
juvenile hypophosphatasia	1/ 535
idiopathic hypercalcaemia	1/27,500
idiopathic hypercalciuria	1/ 106

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Evolution of familial hypophosphataemic rickets during the first two years of life.

A hypophosphataemic mother gave birth to a clinicaly normal boy. The serum values in the cord blood and at 3 weeks of age were: Ca 11.9 and 9.8 mg%, P 4.7 and 3.6 mg%, iPTH 15 and 25 ng/ml (upper normal limit: 40 ng/ml). Rickets appeared at 8 weeks. Treatment with 4 x 1 g neutral Na-phosphate per day during 6 weeks, without Vitamin D, resulted in a rise of serum P to 5.6 mg%, a borderline hypocalcaemia of 8.5 mg% and secondary hyperparathyroidism (iPTH 122 ng/ml), but had no influence on the development of rickets. The addition of 0.25 up to 1.75 mg/day of Vitamin D_2 produced a rise of serum Ca to the upper normal limit, a normalisation of iPTH, and an improvement of the rickets. The continued treatment with Vitamin D and oral phosphate during the following two years maintained reasonable but labile serum P-levels, only slightly increased alk.phosphatase levels and a partial control of metaphyseal rickets. However, we failed to prevent the development of the typical fluffy trabecular bone structur, the bowing of the legs and the slowing-down of the growth rate from the 75th percentile at the age of 6 months to the 10th percentile at 2 years.