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Structural changes of collagen fibrils in skeletal dysplasias

Ultrastructural findings in the iliac crest*

H. Stöß and H.-J. Pesch

Pathologisches Institut der Universität, Krankenhausstraße 8–10, D-8520 Erlangen, Federal Republic of Germany

Summary. The skeletal dysplasias are constitutional, generalized or localized disorders of the skeletal system involving a disturbance of growth and/or bone density; their genetic transmission varies. Pathomorphologically, a combined functional-structural disturbance of the cartilaginous and/or bone tissue is present. Clinically, the result is varying degrees of dwarfism.

Within the framework of a systematic examination of skeletal dysplasias, a total of 84 iliac crest specimens/biopsies obtained from stillborn infants and patients varying in age from a few days to 40 years, were investigated in the electron microscope. The sections prepared extended from the perichondrium through the proximal resting zone to the primary mineralization zone. The structure of the collagen fibrils was studied in diastrophic dysplasia, pseudoachondroplasia, the WOLCOTT-RALLISON syndrome, osteogenesis imperfecta, and idiopathic juvenile osteoporosis.

In diastrophic dysplasia, pseudoachondroplasia and idiopathic osteoporosis, the cartilaginous ground substance contains collagen fibrils that can vary considerably in length, structure and diameter. In one case of WOLCOTT-RALLISON syndrome, the lacunae of the chondrocytes are found to contain very wide amianthoid-like and inadequately aggregated collagen fibrils. In numerous cases, osteogenesis imperfecta reveals very fine and also irregularly structured collagen fibrils with scarcely discernible cross-striation in the region of the osteoid, which is of varying width. In some of the cases, catechin has a favourable effect on the formation of collagen fibrils, resulting in broader and more densely packed fibrils. In addition, the conditions are associated with considerable intracellular changes in the rough endoplasmic reticulum, the Golgi apparatus and the mitochondria.

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Offprint requests to: H. Stöß at the above address

The varying collagen fibril findings in the cartilage and bone tissue also represent a morphological marker of the combined functional-structural disorder of chondrocytes and/or osteoblasts, and an expression of the differing aetiopathogenesis.

Key words: Skeletal dysplasia – Diastrophic dysplasia – Pseudoachondroplasia – Osteogenesis imperfecta – WOLCOTT-RALLISON Syndrom

Introduction

The skeletal dysplasias are constitutional, generalized or localized diseases of the skeletal system with a disturbance of growth and/or bone density. These diseases are usually genetically determined with a variable mode of inheritance, predominantly autosomal dominant or autosomal recessive. To date, they have been classified exclusively on the basis of clinical and radiological findings, with no account being taken of their pathogenesis. In accordance with the "Paris Nomenclature" revised in 1983 by the European Society for Paediatric Radiology, these entities are subdivided into six main groups containing numerous sub-groups (Table 1). The leading clinical feature is disproportionate dwarfism of varying degree, accompanied by deformation of the vertebral column and the extremities, which can manifest within the uterus or after birth. Pathomorphologically, a combined functional-structural disturbance of cartilage and/or bone tissue is found (Stöss et al. 1982), which can be either intracellular or extracellular in origin.

So far, more attention has been directed towards the intracellular disorders of the chondrocytes and osteoblasts (Rimoin 1975; Stanescu et al. 1977; Sillence et al. 1979) than towards the extracellular changes in the cartilaginous and bony ground substances. In this article, our attention has been focussed on the collagen fibrils, as an ordered component of the ground substance, taking diastrophic dysplasia, pseudoachondroplasia, the WOLCOTT-RALLISON syndrome, osteogenesis imperfecta and idiopathic juvenile osteoporosis as examples.

Material and methods

A total of 84 iliac crest specimens or biopsies were obtained from stillborn infants and patients varying in age from several days to 40 years, with diastrophic dysplasia, pseudoachondroplasia, WOLCOTT-RALLISON syndrome, osteogenesis imperfecta, or idiopathic juvenile osteoporosis. After fixation in buffered, 1% glutaraldehyde/4% formaldehyde solution (Trump and Jones 1978), the non-decalcified iliac crest specimens were cut into consecutive slices ranging, in accordance with the growth zone, from the perichondrium via the proximal resting zone to the distal zone of primary mineralization, and investigated zone by zone. After post-fixation in 1% osmic acid, the specimens were dehydrated in increasing concentrations of acetone, block-contrasted with phosphotungstic acid and uranyl acetate, and then embedded in low-viscosity epoxy resin (Spurr 1969), using a technique modified by Schulz (1977). The blocks of resin were then cut with the aid of a Dupont diamond knife to provide ultra-thin sections, post-contrasted with uranyl acetate and lead citrate, and investigated in an Elmiskop 101 electron microscope.

Table 1. "Paris" international nomenclature of constitutional diseases of bone (Ann. Radiol. 26 (1983) 456)

1. Osteochondrodysplasias
1. Defects of growth of tubular bone and/or the spine, with manifestation
a) at birth
b) in later life
2. "Anarchistic" development of cartilage and fibrous tissue
3. Anomalies in the bone density of cortical diaphyseal structures, and/or metaphyseal modelling defects
II. Dysostoses
1. Dysostoses with cranial and facial involvement
2. Dysostoses with predominantly axial involvement
3. Dysostoses with predominant involvement of extremities
III. Idiopathic osteolyses
IV. Miscellaneous disorders with osseous involvement
V. Chromosomal aberrations
1. Numerical aberrations
2. Structural aberrations
3. Aberrations of the sex chromosomes
VI. Primary metabolic abnormalities
1. Calcium and/or phosphorus
2. Complex carbohydrates
3. Lipids
4. Nucleic acids
5. Amino acids
6. Metals

Results

1. Diastrophic dysplasia

Diastrophic dysplasia, which is of autosomal recessive inheritance, was distinguished from achondroplasia in 1960 (Lamy and Maroteaux, 1960). It is characterized by short-limbed (micromelic) dwarfism, with a body length of between 80 and 137 cm, clubfoot, kyphoscoliosis of varying degree, an abnormal, so-called "hitchhiker's" thumb, and deformation of the external ear (cauliflower ear) (Spranger et al. 1974). Radiologically, the tubular bones are short, with splayed out metaphyses, flattened epiphyses and irregular vertebral bodies. Since the clinical course of this disease varies so markedly, in the early years of the child's life it is not possible to make any prediction as to the final height of the patient (Rimoin 1975).

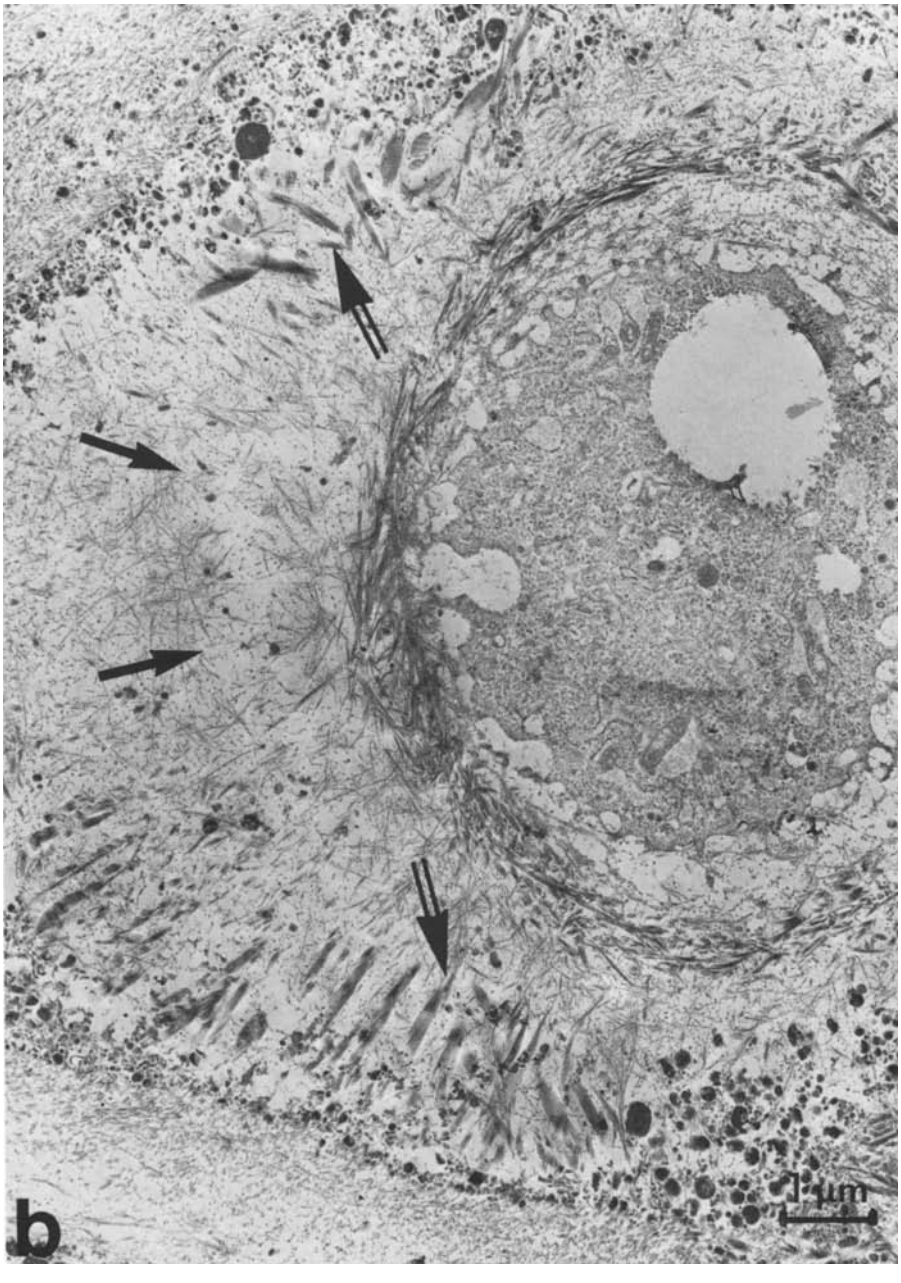
Examinations were done in a 7-year-old boy who, at the time of examination, showed marked dwarfism, and in a 6-month-old girl with largely normal physical development.

The two subjects present differing morphological pictures. In the case of the boy, the chondrocytes are highly reduced in number, and are widely disseminated. In all regions we see degenerating chondrocytes, and pseudocystic changes in the cartilaginous ground substance, which are particularly

Fig. 1. *Diastrophic dysplasia.* **a** Network of collagen fibrils of varying widths, with perifibrillar (→) osmiophilic depositions (EM × 8,000) **b** Circular arrangement of collagen fibrils, some very thin (→), some broadened (⇒), within the lacunae of the chondrocytes (EM × 5,000) **c** Perifibrillar collagen fibrils arranged in single concentric rings (EM × 4,000)

noticeable in the growth plate. Typical proliferation of chondrocytes and columniation are absent.

Some of the cartilaginous matrix is composed of a network of uniformly wide collagen fibrils (Fig. 1a), which usually vary considerably both in length and diameter. In the pericellular area, concentrically arranged atypical collagen fibrils, usually very short in length and varying in width and showing a variability in the periodicity of the cross-striations, are found (Fig. 1b). The collagen fibrils are arranged in several layers, sometimes an-



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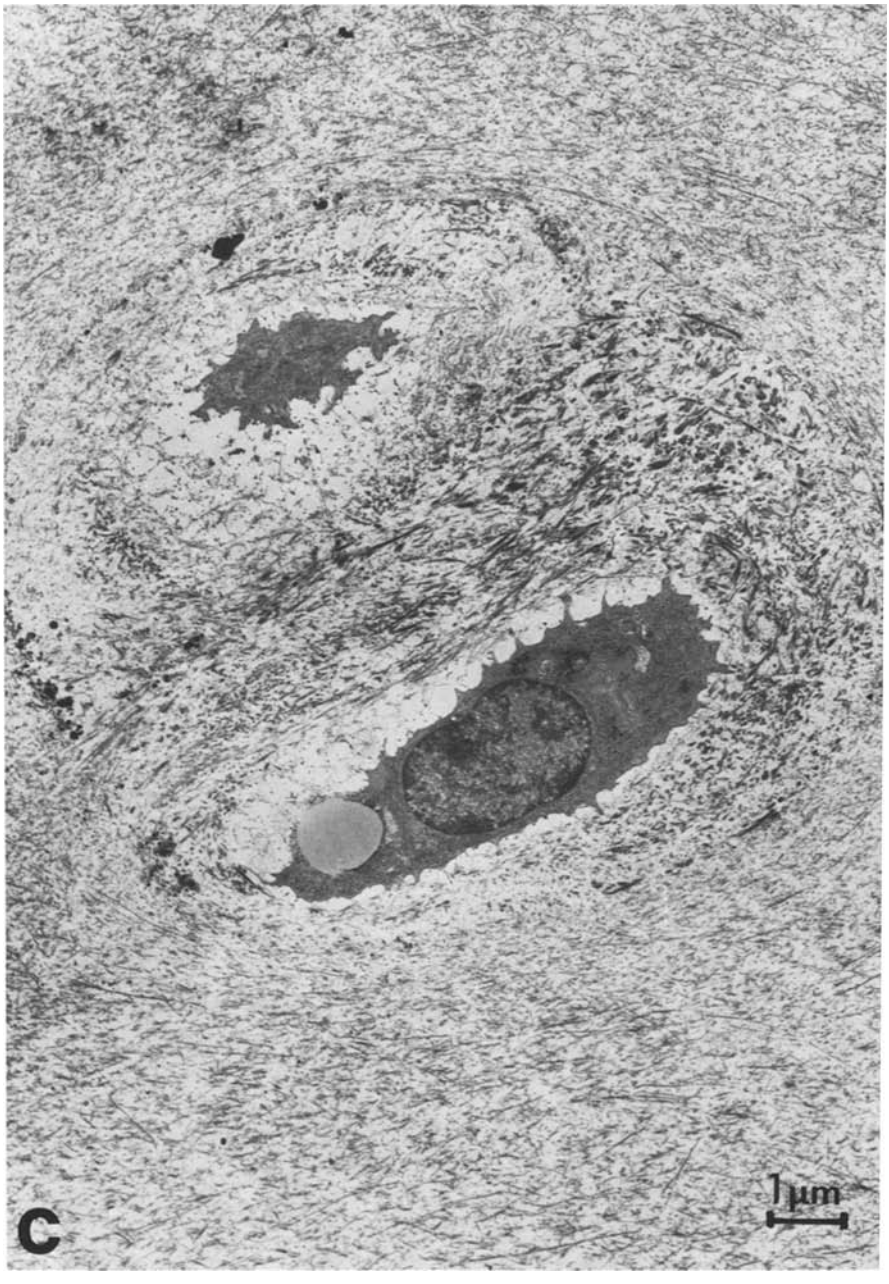
nular in form and "parallel" to the chondrocytes, while sometimes they are arranged perpendicular to the chondrocytes. In addition to very fine thread-like collagen fibrils with hardly distinguishable cross-striation, there are also wide amianthoid-like collagen fibrils revealing cross-striations varying between clearly or vaguely, distinguishable.



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In the 6-month-old girl who, so far, has a largely normal body length, such changes are found only in the resting cartilage. The collagen fibrils show a less marked variation in length and diameter, and are frequently arranged in single concentric rings around the chondrocytes (Fig. 1c). Chondrocyte proliferation and column formation are regular.

2. *Pseudoachondroplasia*

Pseudoachondroplasia was first differentiated from achondroplasia in 1959 (Maroteaux and Lamy 1959). It is probably the second most common form of chondrodystrophy (Hall 1975), and its inheritance is usually autosomal dominant, more rarely autosomal recessive. In the second year of life, a disproportionate, achondroplasia-like dwarfism develops that is characterized by a long trunk, short extremities, normal cranio-facial proportions, and lumbar lordosis. Radiologically, hip joint acetabula are indistinct, and the proximal femoral epiphyses are deformed and diminished in size. The flattened vertebral bodies initially show anterior "tonguing", but later become biconvex, and in adulthood reveal a normal appearance.

Below, the findings of an 11-year-old girl and a 12-year-old boy with the dominant form, and of a 9-year-old girl with the recessive form of pseudoachondroplasia are presented. They all revealed the typical clinical and radiological changes which, however, were less marked in the two children with the dominant form. While in these two children the growth deficit at age 8 was 18 cm, the 9-year-old girl had a deficit of 28 cm at the age of 3 years.

In the case of the dominant form of pseudoachondroplasia, a highly cellular cartilage containing disseminated chondrocytes is found. Chondrocyte proliferation is incomplete, and the columns are sometimes "coarsened", sometimes shortened. The nuclei of the chondrocytes are displaced to the margins of the cells, and the cytoplasm reveals vacuoles, which represent dilated cisternae of the rough endoplasmic reticulum. Some contain a nutmeg-like material which, in the region of the proliferation zone and growth plate, presents a more "fingerprint" appearance.

In some places, the ground substance of the resting cartilage is composed of interwoven collagen fibrils of uniform width. There are also foci of partly widened, partly fine thread-like collagen fibrils (Fig. 2a), accompanied by small osmiophilic particles. At the transition of the resting cartilage to the proliferation zone, both very fine and very wide collagen fibrils with marked cross-striation and numerous sharp kinks can be seen (Fig. 2b). For the most part, the collagen fibrils show a parallel arrangement, and there is only a suggestion of a network. Here, no osmiophilic particles are to be observed. In the region of the growth plate, the collagen fibrils vary considerably in diameter, and have a predominantly longitudinal arrangement. In addition to very fine fibrils, inadequately aggregated fibrils showing only weakly discernible cross-striations can be seen (Fig. 2c). Here, again, osmiophilic particles are found between the fibrils. Furthermore, accumulations of osmiophilic particles are also to be seen between the fibrils, presenting a layering appearance similar to the intracellular changes.

Similar findings are not observed in the recessive form of the condition, where the cartilage is clearly less cellular. Typical chondrocyte proliferation and cartilaginous columns are lacking. In the growth plate, the cartilaginous ground substance shows focal areas of demasking. It comprises either very thin, or very wide, long collagen fibrils which, section-wise, show a parallel

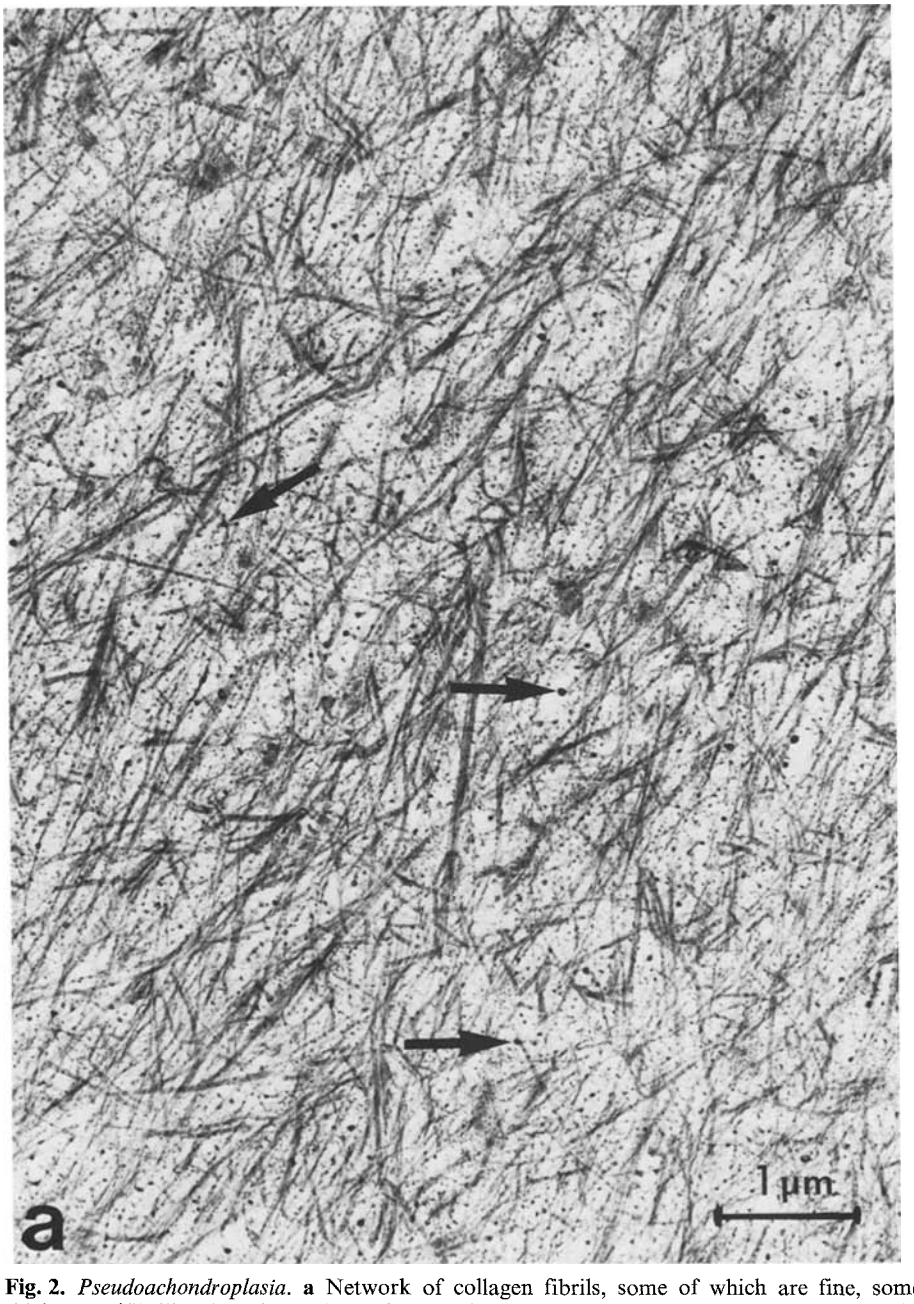
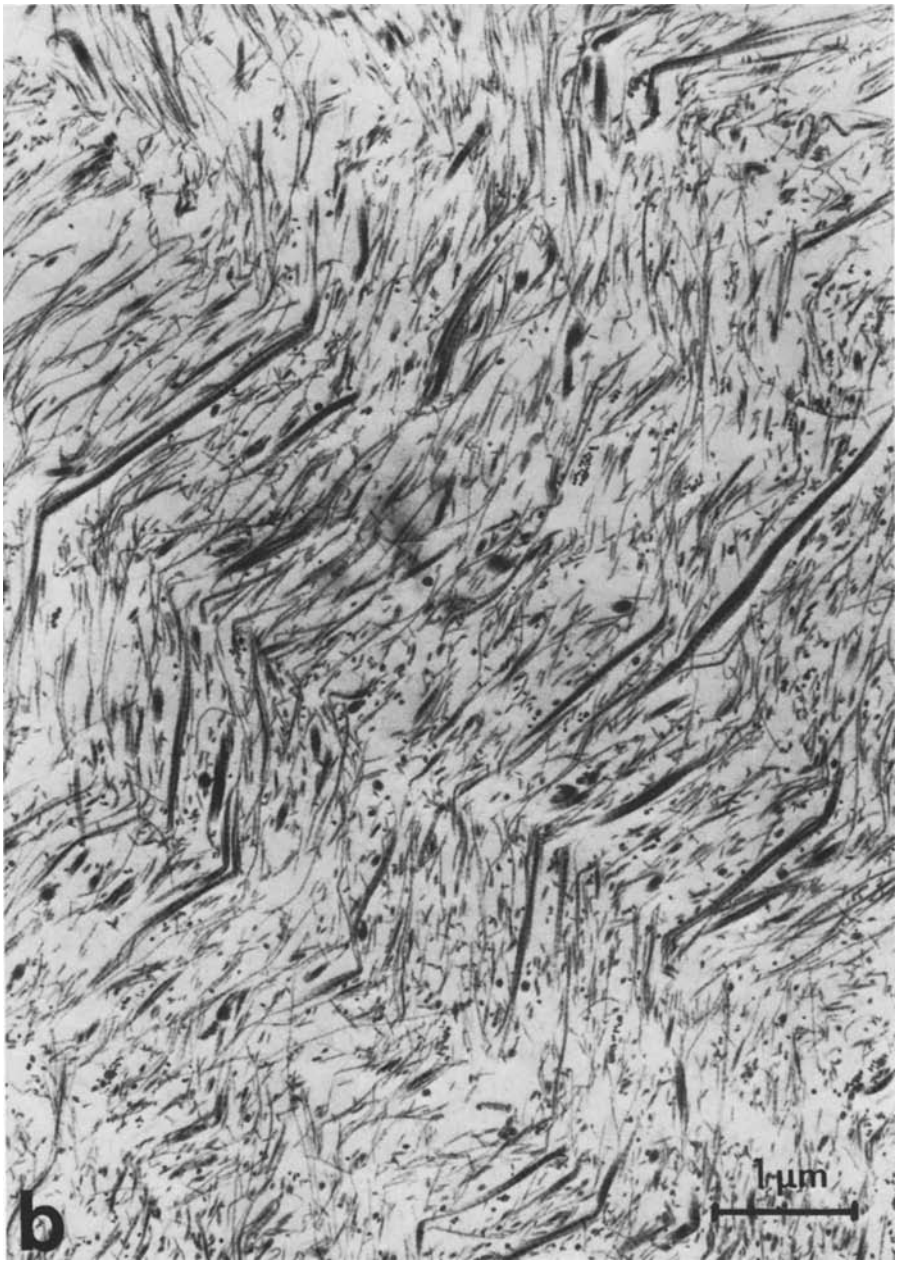


Fig. 2. *Pseudoachondroplasia.* **a** Network of collagen fibrils, some of which are fine, some thicker. Perifibrillar depositions (→) of osmiophilic particles (EM ×8,000). **b** Largely parallel alignment of collagen fibrils with marked cross-striation and numerous kinks (EM × 8,000). **c** Layered depositions (*D*) between varyingly wide, largely thin, collagen fibrils with parallel alignment (EM ×30,000)



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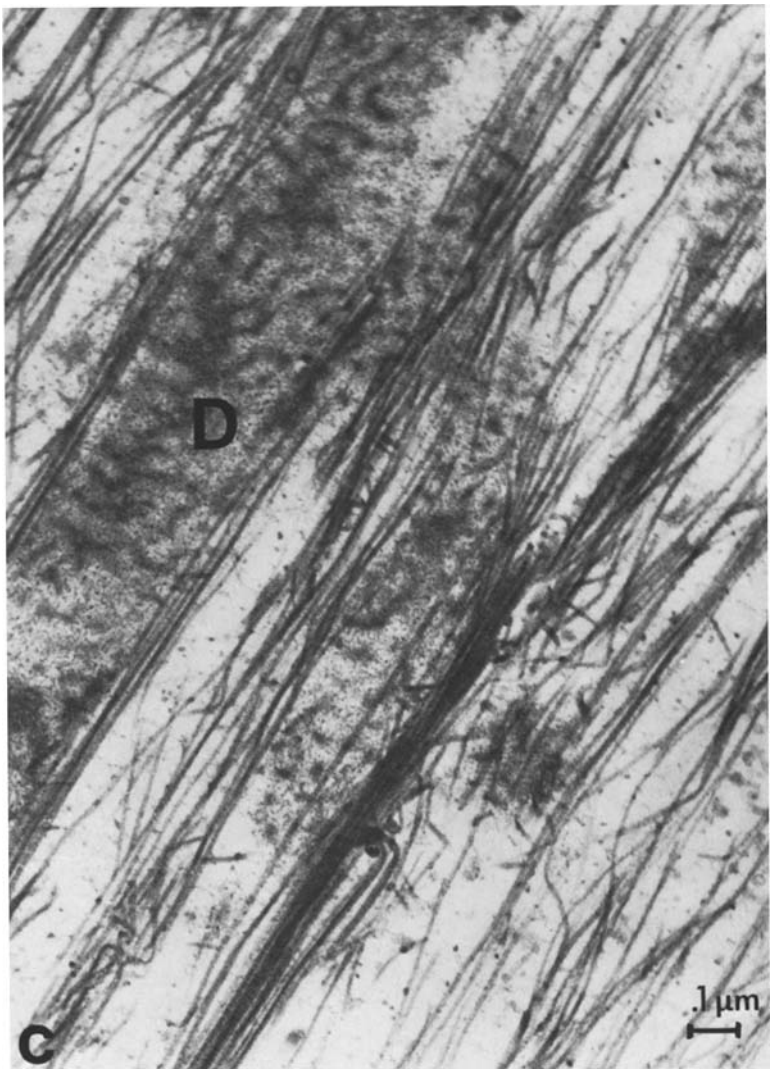
arrangement. These long collagen fibrils frequently reveal inadequate aggregation of the individual components, and an absence of cross-striation.

3. Wolcott-rallison syndrome

The very rare WOLCOTT-RALLISON syndrome was first described in 1972, and is of autosomal recessive inheritance. Clinically, the combined



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occurrence of multiple epiphyseal dysplasia and congenital diabetes mellitus leads to a high-grade disproportionate dwarfism. Radiologically, the tubular bones reveal irregular epiphyses, with premature median ossification, and the vertebral bodies are flattened and irregularly delimited. The acetabula of the hip joints are hypoplastic; the small, irregular proximal epiphyses of the femora are, as in dysplasia of the hip, displaced laterally.

Examinations were carried out in a 13-year-old girl with the WOLCOTT-RALLISON syndrome, who presented with high-grade disproportionate, short-trunk dwarfism, and short extremities. Since the age of 5 weeks, an insulin-dependent diabetes mellitus has been known, which is controlled by "intermediate-acting" insulin.

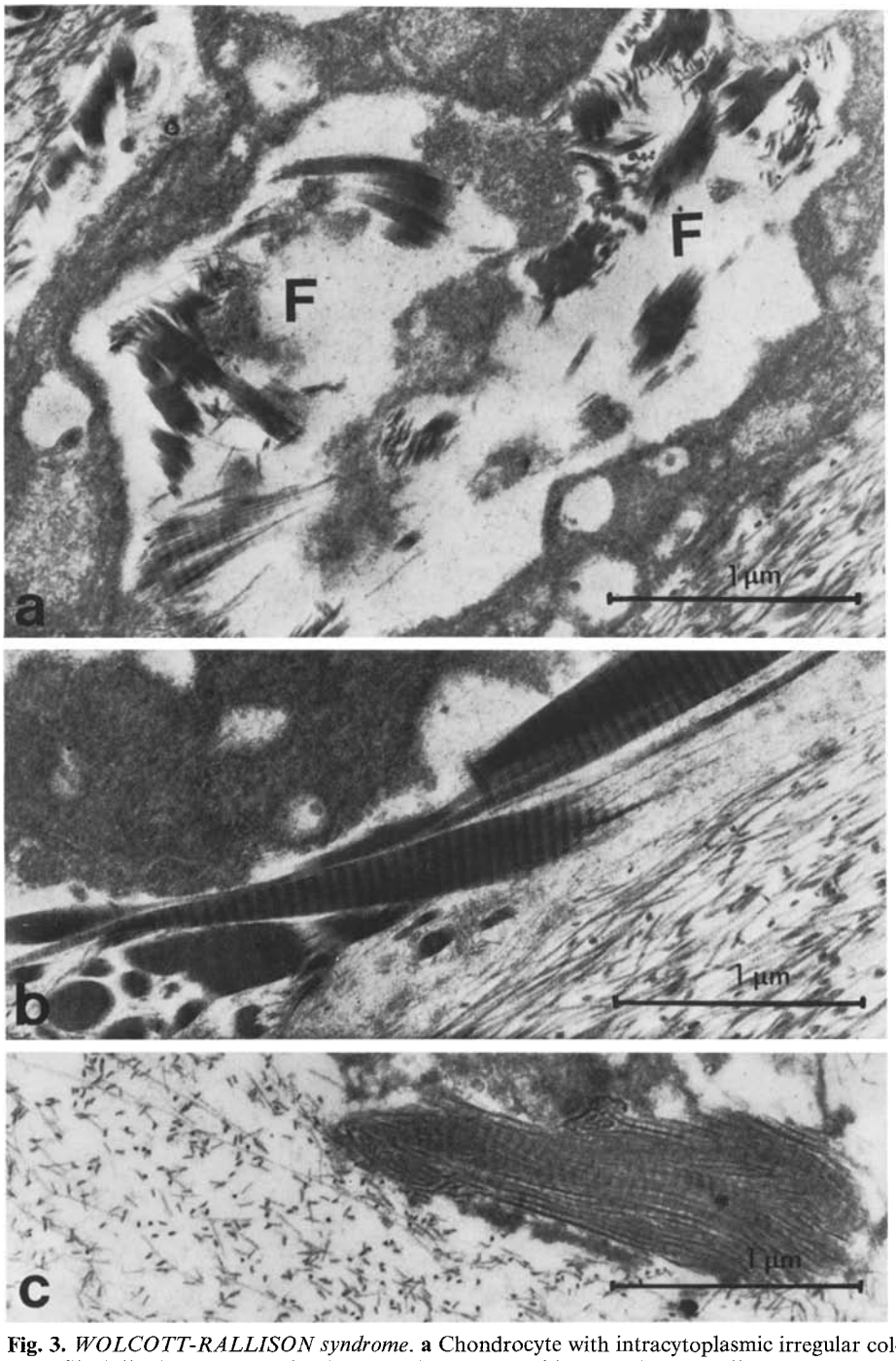


Fig. 3. *WOLCOTT-RALLISON syndrome.* **a** Chondrocyte with intracytoplasmic irregular collagen fibril-like (*F*) structures (EM ×20,000) **b** Greatly widened amianthoid-like collagen fibrils in perichondrocytic location (EM ×20,000). **c** Inadequately aggregated collagen fibrils with sharply delimited cross-striations (EM ×20,000)

The cartilage has very few cells, comprising large-bodies or spindle-shaped chondrocytes. Chondrocyte proliferation and columniation are absent.

The chondrocytes possess a dilated rough endoplasmic reticulum and an enlarged Golgi apparatus with dilated vesicles. They contain an accumulation of short, coarse, irregularly arranged, fibrillary collagen-like structures, some of which are faintly striated (Fig. 3a). The surrounding cartilaginous ground substance is largely composed of irregularly arranged collagen fibrils. Both interwoven uniform and loosely arranged fibrils with considerable irregularities of diameter, are seen. The lacunae are filled either partially or completely with largely concentrically arranged atypical collagen fibrils (Fig. 3b and c) which vary considerably in both length and width. Numerous collagen fibrils, reminiscent of amianthoid fibrils, have an irregular cross-striation, which to sometimes sharply drawn and sometimes indistinct (Fig. 3b). Scattered, inadequately activated collagen fibrils which have largely lost their cross-striation are also seen (Fig. 3c).

4. Osteogenesis imperfecta

Osteogenesis imperfecta (O.i.) is a generalized disorder of the connective and supporting tissues (Bauer 1920), which is probably based on a disturbance of collagen synthesis and an insufficiency of the osteoblasts, resulting in an inadequate production of osteoid and bone. Its inheritance is either autosomal recessive or autosomal dominant. Clinically, the condition is characterized by an abnormal brittleness of the bones, and a varyingly marked blue discolouration of the sclerae. Radiographically, there is generalized osteopenia, and wormian bones are found in the skull. On the basis of the clinical and genetic heterogeneity, the variable symptomatology and prognosis, O.i. is now clinically classified into four types (Sillence et al. 1979).

Examinations were performed in 75 specimens obtained from stillborn infants and patients of both sexes aged between several days and 40 years. In the Sillence classification, the cases comprised 12 Type I, 9 Type II, 15 Type III, 20 Type IV O.i., while in 19 cases, the clinical type was not known. Fifteen children were treated with catechin, and the effects of the treatment monitored on the basis of biopsies obtained prior to and during therapy. In three children, in addition to the usual symptomatology, hyperplastic callus formation was also present.

No specific morphological findings can be correlated with the Sillence clinical classification of O.i. All the O.i. cases examined do, however, have 5 ultrastructural criteria in common: The osteoblasts possess swollen mitochondria, the cisternae of the rough endoplasmic reticulum are dilated, the enlarged Golgi apparatus contains dilated Golgi vesicles, the osteoid zone is narrowed to a varying degree, and mineralization is reduced, both diffusely and in patches in different parts. Amorphous or crystalline deposits are also observed.

Among the cases investigated, a normally developed cartilaginous tissue was found only in the lethal O.i. Type II, and in Type III. In the case

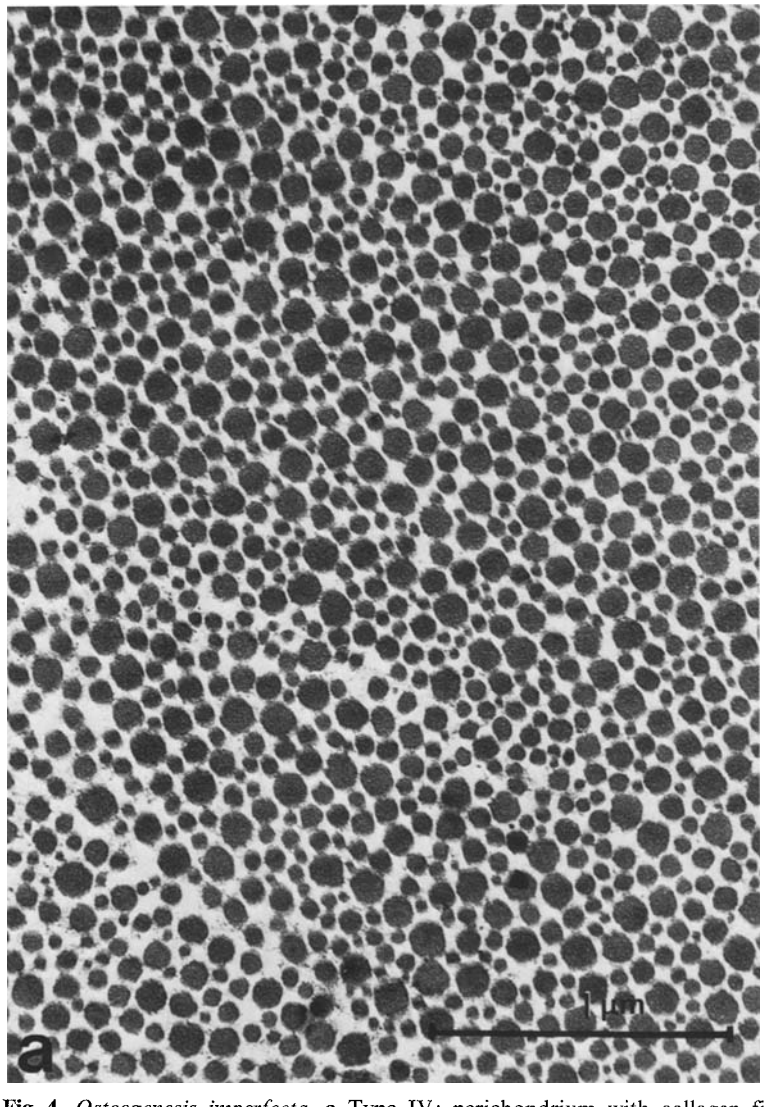
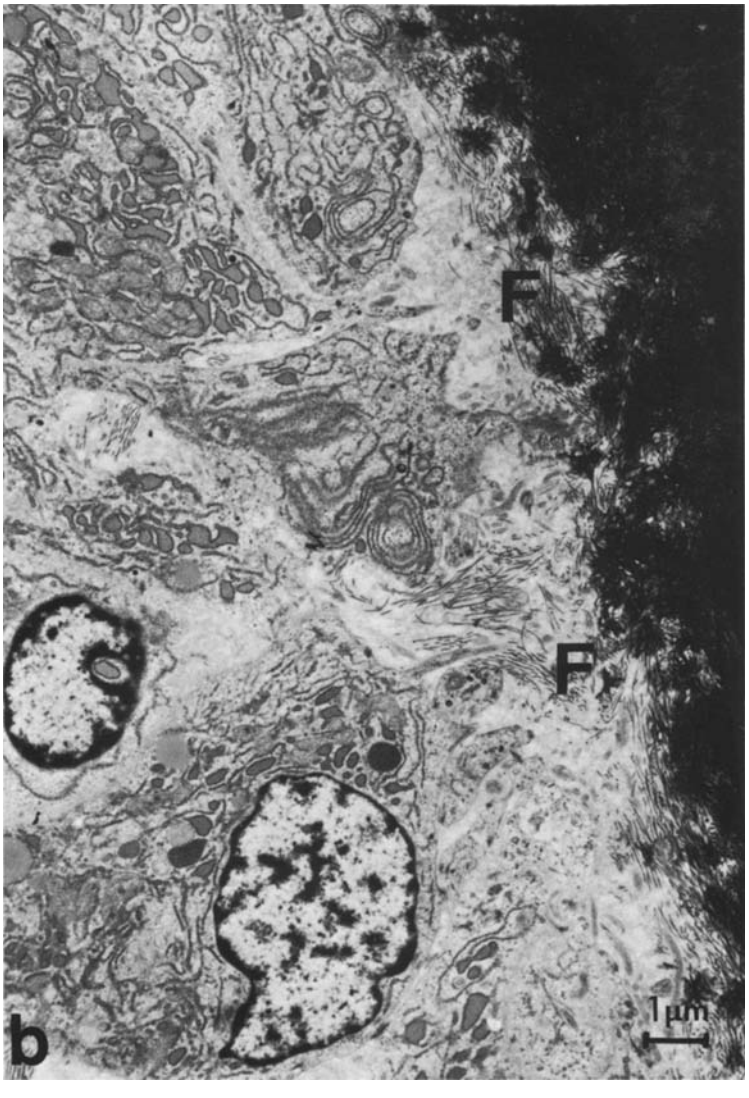


Fig. 4. *Osteogenesis imperfecta.* **a** Type IV: perichondrium with collagen fibrils of varying diameters (EM ×20,000) **b** Type II: a few scattered collagen fibrils (*F*) in the region of the osteoid (EM ×4,000) **c** Type III: fine, unordered collagen fibrils (*F*) in the region of the osteoid with only a suggestion of cross-striation and patchy amorphous mineralization (EM ×8,000). **d** Type III: ordered but loosely arranged collagen fibril bundles (*F*) in the region of the osteoid (EM ×6,000). **e** Type III: fragmented, very loosely arranged collagen fibrils (*F*) in the region of the osteoid (EM ×8,000). **f** O.i. with hyperplastic callus formation: dense bundles of irregularly structured collagen fibrils (*F*) in the region of the osteoid (EM ×20,000)

of the lethal Type II, adjacent to the closely associated cartilage columns, fine, delicate spongy bone trabeculae are seen, which contain abundant non-mineralized residual cartilage. Typically, in the lethal form of O.i., tiny microfractures with desmochondral fracture callus are found in the immediately sub-chondral region.



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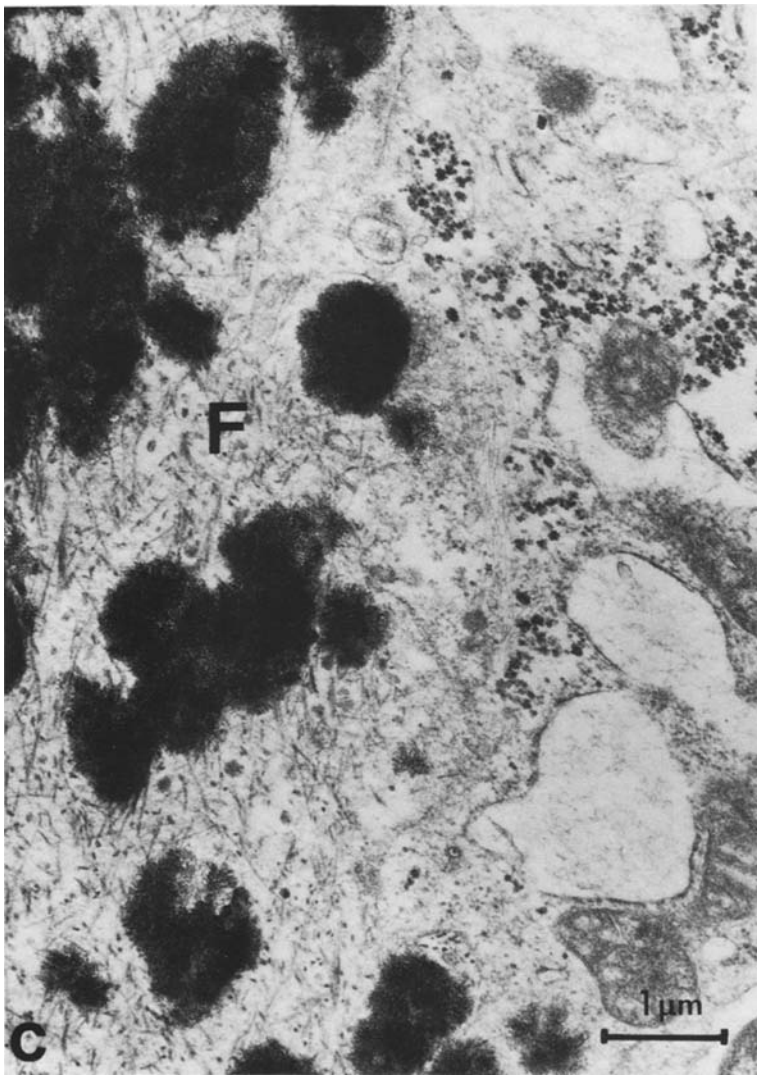
Predominantly in Type IV O.i., but occasionally also in Type I, normally developed cartilaginous tissue may be accompanied by disorganized development in the growth plate, with inadequate chondrocyte proliferation, and only local columniation. The cisternae of the rough endoplasmic reticulum of the chondrocytes are dilated to varying degrees, and in 4 cases the cytoplasm shows vacuolar inclusions similar to those seen in lysosomal storage disease.

Accordingly, not only the collagen fibrils of the bone tissue, but also those of the cartilaginous tissue, are pathologically changed. In numerous cases, in the region of the perichondrium, their cross-striations vary in size (Fig. 4a), while in the cartilaginous ground substance, some are kinked,



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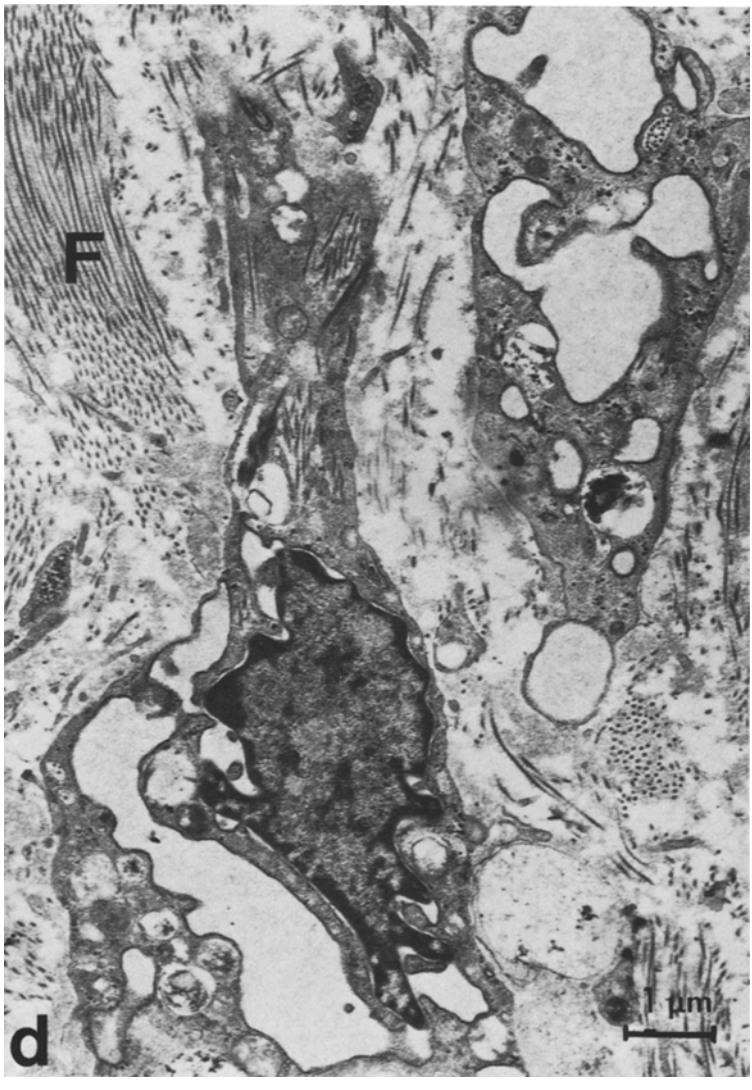
and others vary in length and width. In the osteoid, the collagen fibrils are reduced in number to a varying degree. This reduction is particularly marked in the case of the lethal Type II O.i., where, in some sections, only a few scattered fibrils are to be seen (Fig. 4b). In the case of the "surviving" Types I, III and IV, the collagen fibrils reveal highly heterogeneous changes which, however, do not correlate with the clinical type of O.i. Thus, in the very severe cases, the collagen fibrils are considerably reduced in number, as is the case with the lethal Type II; some of the fibrils are very thin and irregularly arranged, and show hardly any cross-striation (Fig. 4c), while others are ordered, cross-striated, but less closely "packed" (Fig. 4d).



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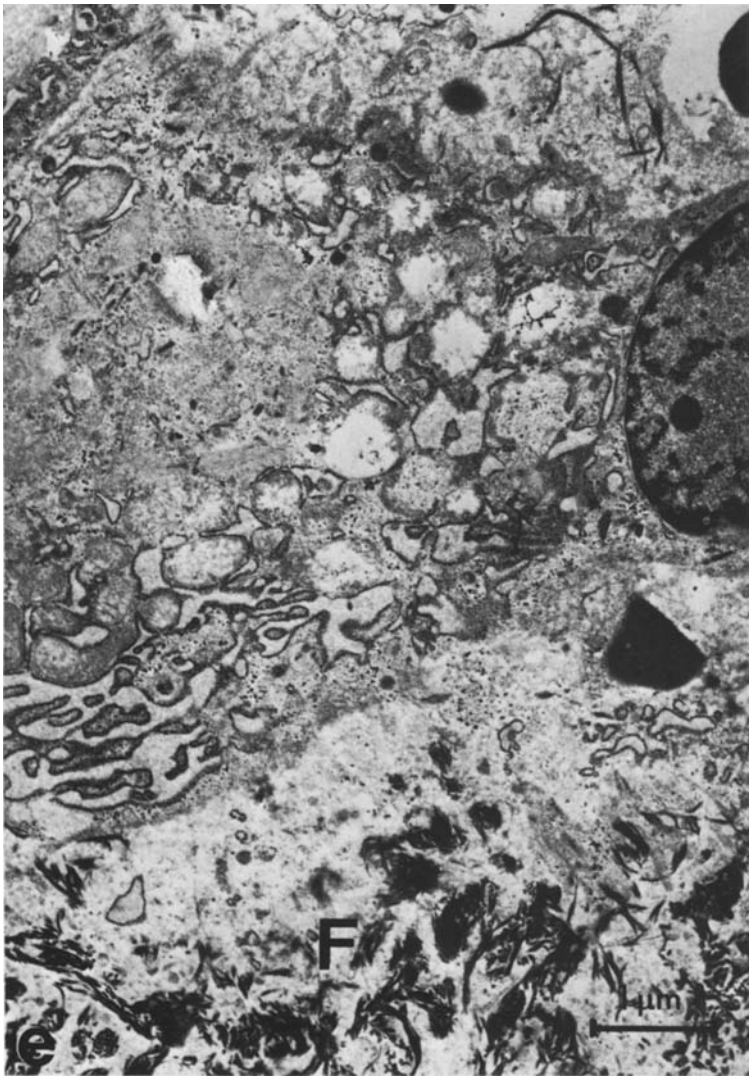
In one case with no striking clinical features, the osteoid is, in part, built up of very short fragmented collagen fibrils which, in some sections are arranged very loosely in the form of "islands", and reveal "fraying" of the ends (Fig. 4e).

In some of the cases of O.i., collagen fibril formation can be favourably influenced by the flavonoid, catechin. Prior to the institution of treatment, the fibrils are reduced in number and frequently irregularly arranged. In 8 out of 15 cases thus treated, follow-up biopsies during treatment showed a widening of the osteoid zone with a dense arrangement of collagen fibrils. For technical reasons, three follow-up biopsies could not be evaluated.



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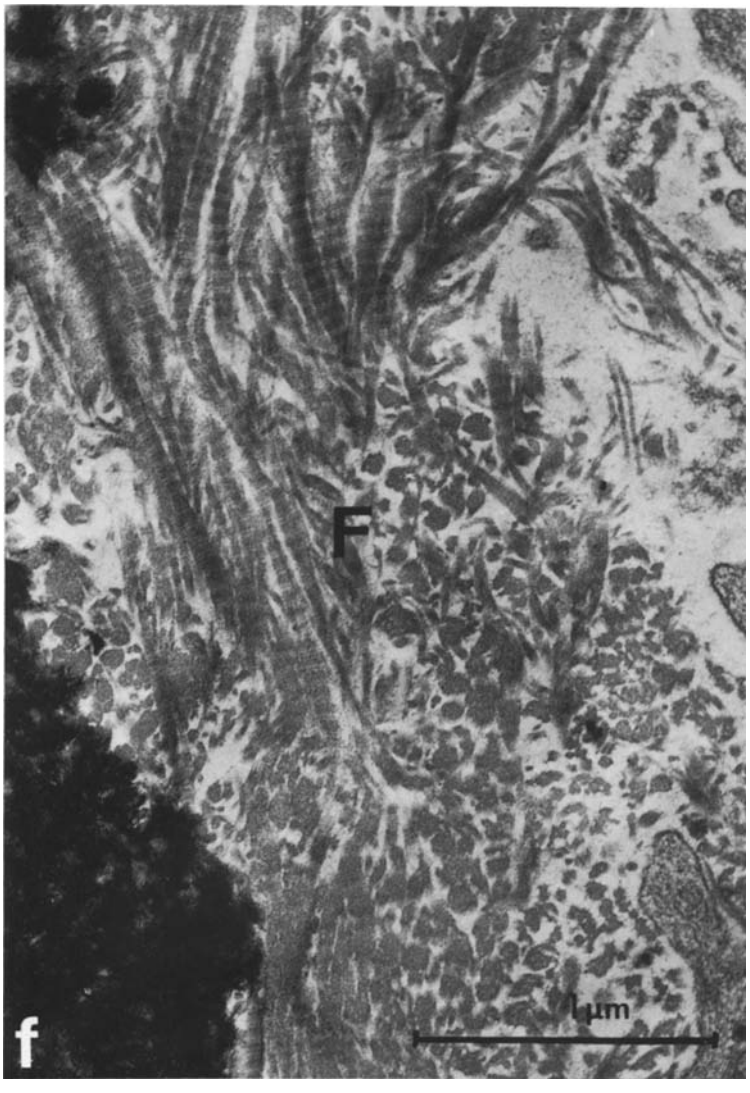
In the 3 cases with hyperplastic callus formation, the osteoid is, locally, very broad, and composed of dense, interwoven bundles of collagen fibrils with marked cross-striation and greatly varying diameters (Fig. 4f).

5. Idiopathic juvenile osteoporosis

Idiopathic juvenile osteoporosis occurs sporadically at about the age of 12–15 years. Genetic determination is so far unknown. Clinically, high-grade osteopenia with bone pain and enhanced brittleness of the bones presents. Radiologically, generalized osteoporosis is particularly marked in the verte-



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bral bodies. As a result, secondary lumbo-dorsal kyphoscoliosis occurs, which may be highly progressive, and the long tubular bones may become deformed. In late adolescence, the osteopenia disappears again. The further prognosis is determined by the skeletal deformation that has occurred in the intervening period.

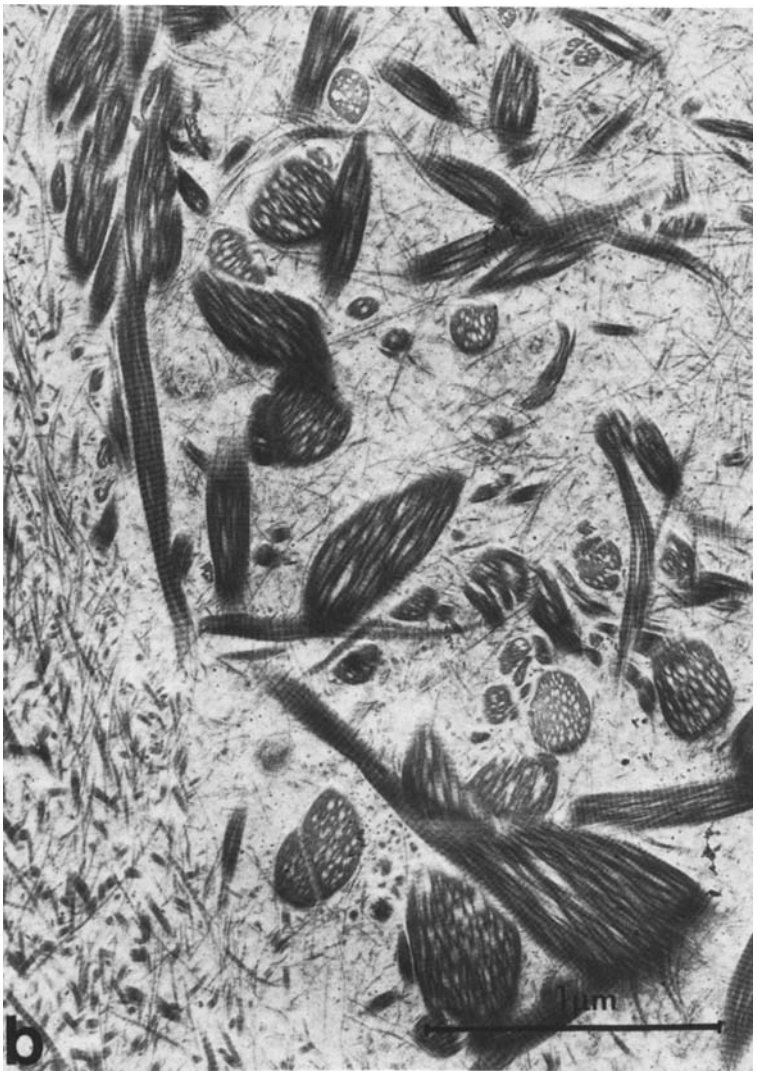
Three male patients aged between 12 and 15 years, who had spontaneously developed progressive osteopenia in early adolescence, were investigated. Osteogenesis imperfecta had been excluded both clinically and morphologically.

The chondrocytes, which in certain sections are reduced in number, show a disseminated distribution. The growth plate is irregular in structure, com-

Fig. 5. *Idiopathic juvenile osteoporosis.* **a** Varyingly wide collagen fibrils with evident cross-striation (EM ×20,000). **b** Markedly broadened, partially dissociated collagen fibrils (EM ×20,000)

prising mostly short, coarse columns of chondrocytes, adjacent to which, non-aligned primary bony trabeculae are to be seen. In addition to chondrocytes with normal configuration, the growth plate also contains increased numbers of degenerating and necrobiotic chondrocytes and varyingly dense cell detritus, in which organelles can sometimes just be made out.

The cartilaginous matrix is non-homogeneous, comprising collagen fibrils varying from very fine to very considerably broadened, with some showing "fraying" of the ends. A clearly recognizable cross-striation is



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to be seen only in the wide collagen fibrils (Fig. 5a); in addition, in all sections of the cartilage, areas containing longitudinally aligned collagen fibrils are repeatedly found.

In the proliferation and growth zone, the lacunae contain varying amounts of alternately broad amianthoid-like collagen fibrils of irregular cross-section, some possessing a sharply delimited, some a widened, indistinct cross-striation. In individual lacunae, the collagen fibrils are inadequately aggregated and reveal marked dissociation of the individual filaments. In addition, loosely distributed netlike interwoven fine filament-like collagen fibrils with no cross-striation can be seen (Fig. 5b).

Discussion

The skeletal dysplasias described here belong to the osteochondroplasias, a common feature of which is a varyingly marked complex disturbance of the connective and supporting tissue in part affecting the endochondral bone growth, in part mineralization. Diastrophic dysplasia, pseudoachondroplasia and the WOLCOTT-RALLISON syndrome are characterized by dwarfism of varying degree, which originates in an enchondral disturbance (Rimoin 1975, Maroteaux 1979). Osteogenesis imperfecta and idiopathic juvenile osteoporosis, in contrast, are characterized by a considerable reduction in bone density.

The light- and electron-microscopic changes represent a combined functional and structural disturbance of cartilaginous and bone tissue, and of the growth plate (Stöss et al. 1982). This disturbance originates in a defect of intracellular metabolic processes, which leads to ultrastructural changes in the chondrocytes, osteoblasts and ground substance. In each of the clinical entities represented here, the defect has a different genesis, and thus expresses itself in the structured extracellular ground substance in a variety of ways.

In the case of diastrophic dysplasia, the concentric accumulation of atypical collagen fibrils of highly varied appearance in the cartilaginous tissue is pathognomonic (Stanescu et al. 1977; Horton et al. 1979). These atypical collagen fibrils are a product of a disordered collagen metabolism (Stanescu et al. 1977 and 1980), more recent studies have demonstrated an SLS collagen with an abnormal cross-striation pattern (Stanescu et al. 1982). It is not known to what extent these morpholocial changes and their varying expressivity in the cartilaginous tissue correlate with the final height of the patient. Only long-term observations and repeated biopsies obtained at orthopaedic corrective procedures will be able to show whether the pathomorphological differences in the resting and overall cartilage are dependent on age, or are merely the manifestation of a varying expressivity of the entity (Stöss et al. 1982).

In pseudoachondroplasia, the "fingerprint-like" inclusions, which in the resting cartilage can also present a "nutmeg-like" appearance, are also pathognomonic for the autosomal dominant form. These inclustions represent collections of a protein in the rough endoplasmic reticulum (Stanescu et al. 1977). By means of gel electrophoretic and biochemical investigations, Stanescu et al. (1982) were able to demonstrate that during the course of proteoglycan metabolism, an abnormal core protein is synthesized within the cell. This core protein can probably not be transferred out of the rough endoplasmic reticulum into the Golgi system, so that it remains in the cisternae of the reticulum. This disorder might explain both the inadequate cross-linkage and the formation of very fine collagen fibrils, as also the deposition of unsharply delimited substances with a layered structure found within the cartilage.

In the very rare autosomal recessive form of pseudoachondroplasia, the classical pathognomonic inclusions are absent (Stöss et al. 1982). In cases

whose genetic transmission is unclear, therefore, an iliac crest biopsy can help clarify the mode of transmission.

A peculiarity of pseudoachondrodysplasia is the fact that, although the varying genetic transmission leads to characteristically different morphological changes, the clinical picture is identical, differing only in the degree of its severity.

In the case of the WOLCOTT-RALLISON syndrome, the multiple epiphyseal dysplasia takes a particularly severe course, owing to the congenital diabetes mellitus that belongs to the entitiy (Wolcott and Rallison 1972; Stöss et al. 1980). The pathological changes in the chondrocytes, with dilated endoplasmic reticulum and intracellular inclusions, are an expression of an increased cellular degeneration (Gomy et al. 1980; Stöss et al. 1982). The very broad collagen fibrils are probably amianthoid fibrils (Hough et al. 1973). Abnormally broad collagen fibrils can also be formed in vitro by proteoglycan extraction from the epiphyseal cartilage (Kühn and v. d. Marck 1978). The intracellular fibrillar and collagen-like elements probably arise secondarily on the basis of the functional-structural disturbance of the chondrocytes. Intracellular collagen fibrils are, for example, also found in rheumatoid arthritis (Harris et al. 1977).

Osteogenesis imperfecta (O.i.) and idiopathic juvenile osteoporosis are two diseases of the bone in which more or less marked osteopenia is a major radiological feature. As long ago as 1920, K.H. Bauer considered O.i. to be a systemic disease of the connective and supporting tissue. His hypothesis has, in the meantime, been supported by numerous biochemical studies which have revealed a number of biochemical defects in the metabolism of collagen, but also in the synthesis of proteoglycans (Spranger 1982). In some of the cases of osteogenesis imperfecta, an increase in Type III collagen and a reduction in Type I collagen occurs (Müller et al. 1977; Penttinen et al. 1978). In other cases, an elevated hydroxylysyl content with a reduced lysyl moiety is found (Kirsch et al. 1981). These two changes in collagen metabolism are found primarily in O.i. Types I and II. In addition, a reduction in pro alpha 1 (I) synthesis, the detection of Type V collagen in the bone and abnormal GAG distribution in the dentine, and an increase in non-collagenous bone matrix proteins, have all been reported (see Spranger 1982). The morphological correlate of these biochemical changes is an inadequate formation of collagen fibrils in the region of the osteoid, which is associated with reduced mineralization. The multiplicity of biochemical defects also explains the pathomorphologically heterogeneous findings in the collagen fibrils, not only in the bone, but also in the perichondrium and the ground substance of the cartilage.

The only partially favourable effect of the flavonoid catechin on O.i. (Cetta et al. 1977; Stöss et al. 1979), is based on an improvement in the thermal stability of the collagen fibrils (Pontz et al. 1982 and 1982), and not on an increase in the synthesis of collagen. In contrast, in cases refractory to treatment due to a different biochemical defect a similar stabilizing effect is not possible.

Pathomorphologically, a combined functional-structural disorder of cartilaginous and/or bone tissue is found to underlie the skeletal dysplasias discussed here. Intracellularly, this manifests, in varying degrees, in a dilatation of the rough endoplasmic reticulum, large Golgi apparatuses with dilated sacculi and vesicles, swollen mitochondria and depositions of varyingly electron-dense material in the cell organelles. These disturbances differ both qualitatively and quantitatively from one entity to another. The differing findings in the collagen fibrils of the cartilaginous and bone tissue also represent a morphological correlate of this functional disorder. For this reason, it would appear safe to conclude that a disorder of the uniformed ground substance also exists.

Electron-microscopic investigations of skeletal dysplasias not only expand our knowledge of histological findings, but also establish more clearly the diagnostic differences in the disturbance patterns, and, in addition, can provide valuable information on the pathogenesis of these inheritable diseases. For these reasons, ultrastructural studies should be a matter of course not only in the case of clinically and radiologically unclear clinical pictures, but also in all skeletal dysplasias.

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