Virchows Archiv A Path. Anat. Histol. 362, 129—143 (1974)

Morphological Studies on Pathogenesis of Epiphyseal Slipping in Uremic Children

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Received September 12, 1973

Summary. The epiphyseal growth plate of femora (proximal and distal), tibiae, radii and ulnae of seven uremic children were studied to clarify the histopathogenesis of epiphyseolysis. Epiphyseolysis was found to be result of three different processes: (1) growth arrest, (2) excessive erosion of the growth cartilage and of the trabeculae of metaphyseal spongiosa and (3) disturbance of vascularisation of hypertrophic cartilage. By resorptive destruction, secondary hyperparathyroidism causes loss of the chondro-osseous continuity. The ordered trajectoral pattern of the trabeculae in the primary spongiosa is transformed into a dense lace of mechanically inferior trabeculae consisting of woven bone. Impairment of primary mineralization could not be demonstrated. Intensive subperiosteal osteoclastic resorption leads to a reduction of metaphyseal width and to fractures of the unsupported lateral parts of the growth cartilage. There were notable differences between the growth plates in different localisations: in growth plates subjected to axial compression (distal femur, tibia) signs of growth arrest prevailed (reduction of hypertrophic cartilage, occlusion of the growth plate by a transverse plate of bone); in growth plates subjected to shearing forces (upper femur, radius, ulna) epiphyses were seen to slip sideway.

Uremic osteodystrophy in children is a disease of the growing skeleton. Therefore striking abnormalities are found in the growth plates. Consequently, impairment of skeletal growth is an outstanding feature of the disease, that has been well known for decades (Fletcher, 1911; Barber, 1920; Brockman, 1926; Hamperl, and Wallis, 1933; Welz, 1936; Kluge, 1937; Köhn and Gelinski, 1942). Epiphyseolysis is a common clinical problem in severe renal osteopathy (Pearson, 1927; Brailsford, 1933; Shea and Mankin 1966; Fine *et al.*, 1970; Cattell *et al.*, 1971). In agreement with Kirkwood *et al.* (1972) we found evidence of epiphyseolysis in 3 out of 85 dialysed uremic children and in 5 out of 20 non dialysed uremic children (Mehls *et al.*, 1973). Previous reports on the morbid anatomy in the skeleton of uremic children clarified that both malacic and fibro-osteoclastic features occur in renal osteodystrophy (Hamperl and Wallis, 1933; Follis, 1950). While numerous studies deal with the roentgenological aspects of epiphyseolysis in children with chronic renal failure (Brailsford,1933; Schinz, *et al.*, 1952; Stanbury, 1957; Shea and Mankin, 1966; Cattell *et al.*, 1971; Kirkwood *et al.*, 1972). the underlying morphological lesions in the growth plates have not been systematically investigated so far. Therefore the pathogenesis of epiphyseolysis in uremia is still under discussion. A careful anatomical analysis

* With support of Deutsche Forschungsgemeinschaft. Presented in part at the Annual Meeting of the European Society for Pediatric Research, Heidelberg 1972.

Table 1

No.	Age (years)	Sex	Cause of uremia	Duration of renal insufficiency (serum creatinine < 2 mg-%)
329/72	5	♂	juvenile nephronophthysis	28 months
494/73	8	♀	obstructive uropathy	32 months
423/72	10	♀	obstructive uropathy	18 months
383/72	10	♀	hypoplasia of kidney	36 months
659/73	12	♀	haemolytic uremic syndrome	4 months
650/72	12	♂	obstructive uropathy	41 months
390/72	13	♀	familial nephrotic syndrome	29 months

of the structural changes encountered in slipped epiphyses should provide some insight into the underlying pathogenetic mechanisms. This gave us reason to study epiphyseal growth plates of 7 children dying in endstage renal failure.

Material and Methods

Epiphyseal plates (proximal and distal femur, proximal tibia, distal radius and ulna) from 7 children with chronic renal failure (with and without hemodialysis) were removed within 12 hours after clinical death. Specimens were fixed in 70% ethanol, dehydrated, defatted and embedded in methylmethacrylate or in paraplast (after decalcification). Undecalcified sections were stained after Masson-Goldner (modification after Schenk, 1969) with alcian blue—PAS and after von Kossa. Decalcified sections were stained after Masson-Goldner and with hematoxylin eosin. The cases under study are summarized in Table 1. Undecalcified ground sections (100 μ) were studied by microradiography (Philips PW 1120/00/60).

Histological Findings

Whereas qualitatively skeletal lesions were similar in all patients studied, the severity of the lesions varied considerably.

Presumably due to its low turnover rate cancellous bone in the *epiphyses* showed remarkably slight alterations: moderate endosteal fibrosis and osteoclastic resorption, scant osteoid seams. Evidence of disturbed blood supply (aseptic necrosis) was never observed (Fig. 1 a, b).

The overall width of the *epiphyseal growth plates* was not systematically increased: the contour toward the epiphysis was usually smooth and regular. In contrast, the border toward the metaphysis was highly irregular. Zones of disorderly proliferating cartilage alternated with zones, in which the width of the growth cartilage was diminished. Relative to the width of the metaphysis, the horizontal diameter of the growth plate was too large thus riding over the lateral border of the metaphyseal bone (Fig. 1 a and b).

The zone of *resting cartilage* showed no obvious abnormality. However, the columnar arrengement of chondrocytes in the zone of *proliferating cartilage* was seriously disturbed: in contrast to normal columnar cartilage, where chondro-

cytes lie single file one behind the other, chondrocytes in uremic children often were arranged in grapelike clusters, the cells lying side by side. In addition, the regular longitudinal orientation of the columnae was partially lost, the direction of the columnae being deflected laterally presumably in response to shearing forces (Figs. 2a, 3b, 4b).

The zone of *hypertrophic cartilage* was fairly irregular or entirely lacking due to increased chondroclastic activity underneath the cartilage plate (Fig. 4a and b). Generally the zone of *primary calcification* was not disturbed when studied with von Kossa stain or by microradiography (Fig. 6a–d). But in slipped epiphyses its plane often was tilted and no longer congruent with the direction of metaphyseal trabeculae (Fig. 3a).

The most outspoken changes were encountered at the *border between growth cartilage and metaphysis*. The normal sequence of vascular invasion, chondroclastic erosion of calcified chondroid and osteoblastic deposition of bone matrix on primary spongiosal trabeculae was seriously disturbed. At some places the transition between cartilage and metaphysis was represented by an osseous bar occluding the growth plate (zone of growth arrest; Fig. 4c). At other places highly atypical sinusoidal vessels without perithelial cells were encountered underneath the cartilage plate. Orderly vascular invasion between calcified longitudinal bars of chondroid was absent and vascular dense fibrous tissue with numerous fibroblasts was often seen below a sharply demarcated cartilage plate (Figs. 3a and b, 4a and b). The border between cartilage and metaphysis was smoothed by chondroclastic removal of cartilage. Occasionally, excessive chondroclastic activity created cystic excavations between cartilage and metaphyseal bone (Fig. 3a and b; 4a and b).

Underneath the growth cartilage highly irregular trabeculae were found. Unlike primary spongiosa they were formed metaplastically by primitive fibrous osteoblasts from a dense fibrous tissue. They were usually not contiguous with the cartilage, were devoid of a chondroid core and consisted entirely of poorly mineralized woven bone. They lacked the usual trajectorially orientated longitudinal pattern (Figs. 1a and b, 2a, 3b, 4a).

Evidence of microdamage was given by small cracks within the cartilage or between cartilage and metaphyseal tissue. Often the columnae of cartilage and the collagen fibers were aligned parallel to the plane of cleavage (Figs. 2a and b, 3b).

Whereas in normal metaphysis the number of primary trabeculae is sharply reduced by osteoclastic removal at the juncture between primary and secondary spongiosa, a similar reduction was lacking in severe uremia. The trabeculae of *secondary spongiosa* exhibited remarkably few osteoid seams and consisted predominantly of lamellar bone with dissecting fibroosteoclasia (Figs. 1a and b, 2a, 5).

Marked abnormalities were seen at the *periosteal surfaces* of the metaphyses. A continuous layer of cortical bone was no longer recognizable. As a consequence of severe cancellisation of compact bone, only isolated trabeculae, interspersed between fibrous tissue, were encountered (Fig. 1a and b). In bones with slipped epiphyses the periosteal sheath was intact. The collagen fibers at the periosteal

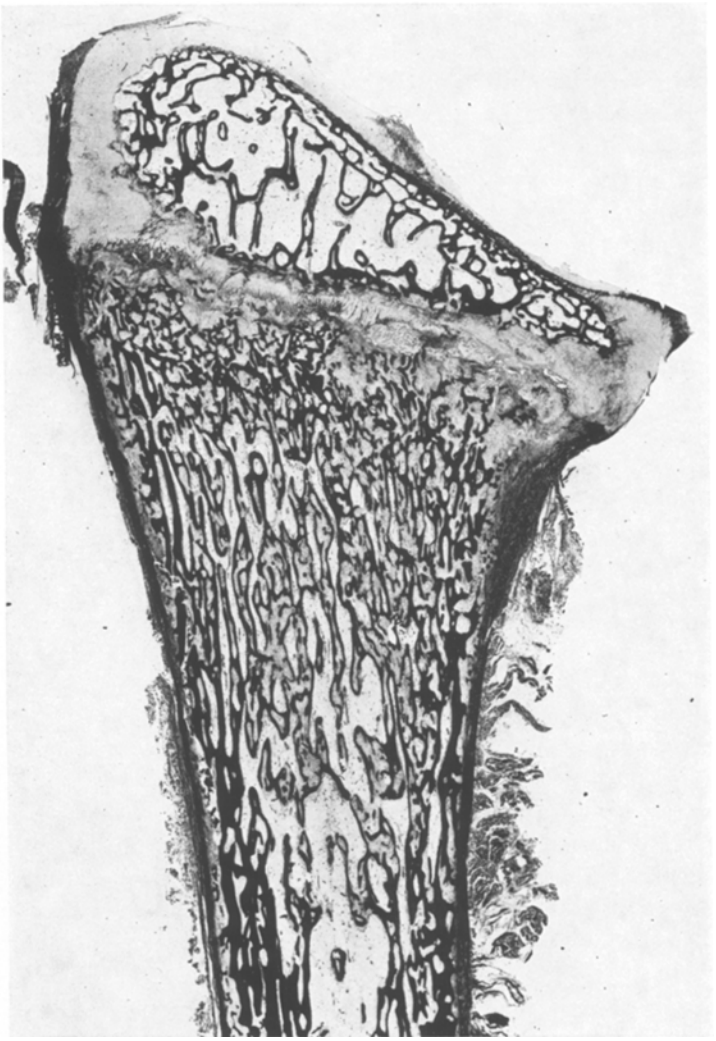
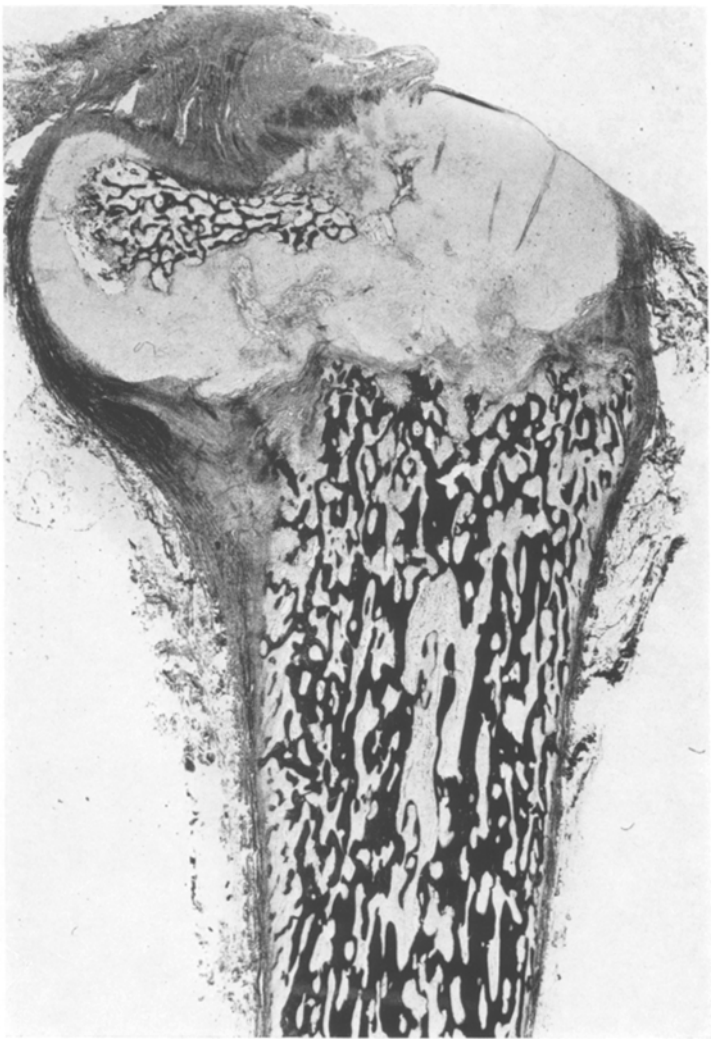


Fig. 1a and b. No. 383/72, 10 y. old girl. a Radius, b Ulna. Epiphysiolysis, irregular cartilage plate. Severe fibroosteoclasia with destruction of primary spongiosa and dissecting cancellisation of cortical bone. Large wedgeshaped area of fibrous tissue underneath the growth cartilage without supporting metaphyseal trabeculae. Microphotograph, Masson-Goldner stain, enl. 1:5

surface had a normal direction. No rupture was seen in the fiber ring constituting the "fibres d'encoche". But occasionally fibers of its inner layer could be seen that ran into the cleavage plane between cartilage and metaphysis (Fig. 2b).

Underneath the growth plate great amounts of fibrous tissue were visible in the lateral metaphysis (appearing as a wedge-shaped area in longitudinal sections) supporting the protruded epiphyses. In the outer part of the cartilage, which was overriding this wedgeshaped area of poorly mineralized fibrous tissue, full thick-



ness ruptures of the cartilage plate were occasionally observed. The gap in the cartilage was invaded by vessels both from the metaphysis and the epiphysis (Figs. 1 a and b, 2a and b).

Evidence of acute traumatic fractures in the metaphyses was never encountered. There were characteristic differences in the behaviour of the epiphyseal plates in various locations. Whereas the tibial and the distal femoral epiphyses, subject to axial compression, were uniformly thinned and occluded by osseous arrest plates, lateral movement (slipping) was usually seen in the upper femoral epiphyseal plates (subject to gravitational shearing forces) and in the ulnar and radial plates (subject to shearing forces due to muscular traction).

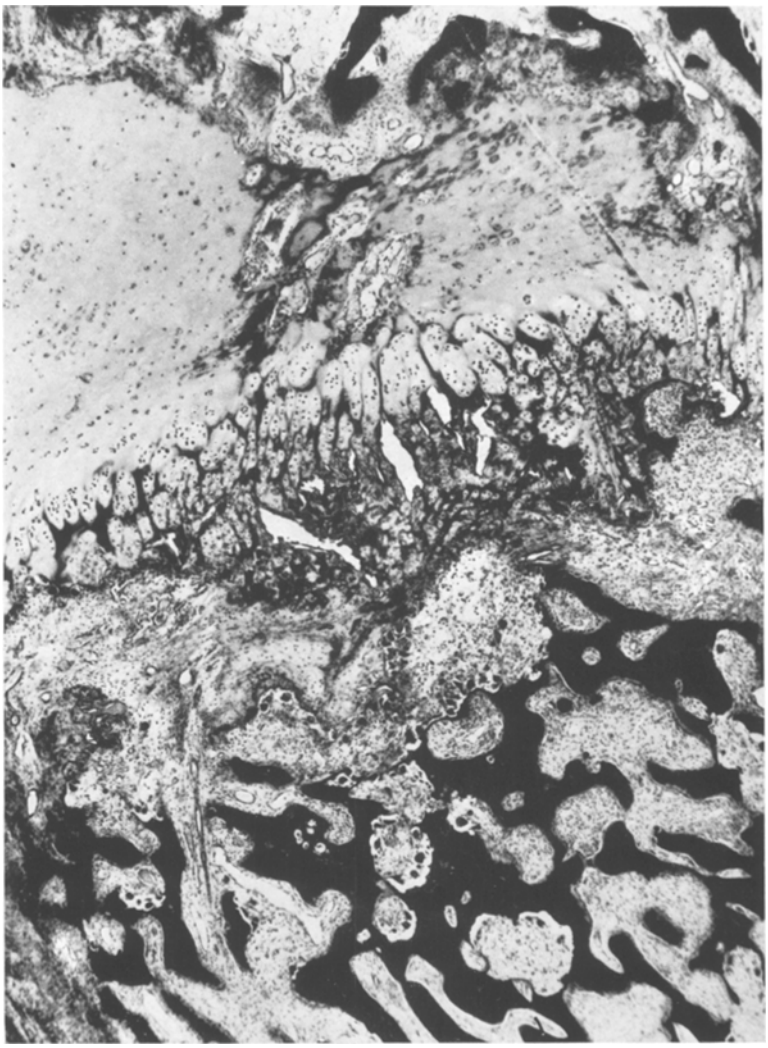


Fig. 2a and b. Detail from Fig. 1. a Longitudinal fracture in the overriding growth cartilage of the radius with invading blood vessels from the epiphysis and the metaphysis. Disorderly orientated cartilage columnae. Marked osteoclastic destruction of the metaphysis. b Lateral aspect of the ulna. Protruded epiphysis overriding the wedgeshaped area of fibrous tissue. No rupture of the fibres d'encoche. Microphotograph, Masson-Goldner stain, enl. a 1:20, b 1:10

Discussion

The above histological studies failed to show a traumatic separation in the metaphyseal region, as has been postulated previously on the basis of roentgenological studies (Kirkwood *et al.*, 1972). On the contrary, epiphyseal slipping was shown to be the result of a coordinated lateral movement of the epiphyseal structure in the wake of intensive destructive and reparative processes at the epi-

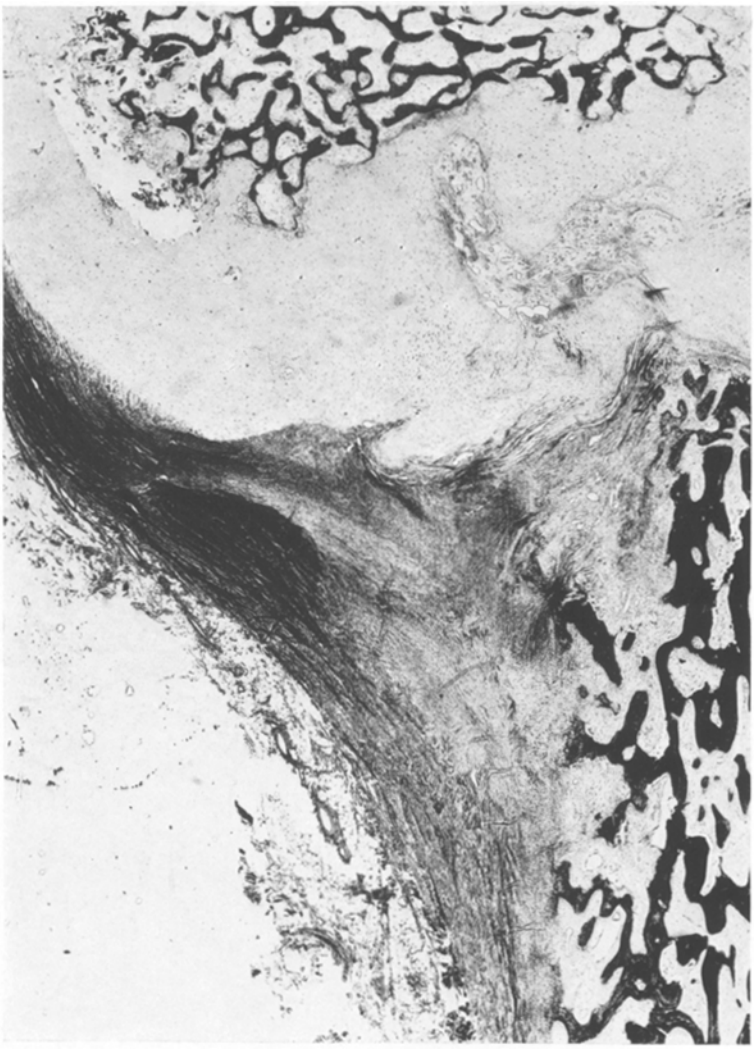


Fig. 2b

physeal-metaphyseal juncture caused by of secondary hyperparathyroidism. Consequently no callus formation was observed. The only evidence of extraneous traumatic forces were small vertical cartilage fractures. The morphological changes underneath the cartilage plate in uremic epiphyseolysis are somewhat comparable to those, that are observed in the socalled "Umbauzone" of tubular bones in the malacic or rachitic skeleton.

The primary fault that ultimately leads to the lateral movement of the epiphysis appears to be the failure of the trabeculae of the primary spongiosa to form a tight stable interlocking complex with the growth cartilage. In advanced cases no connection was observed between the cartilage and the metaphyseal

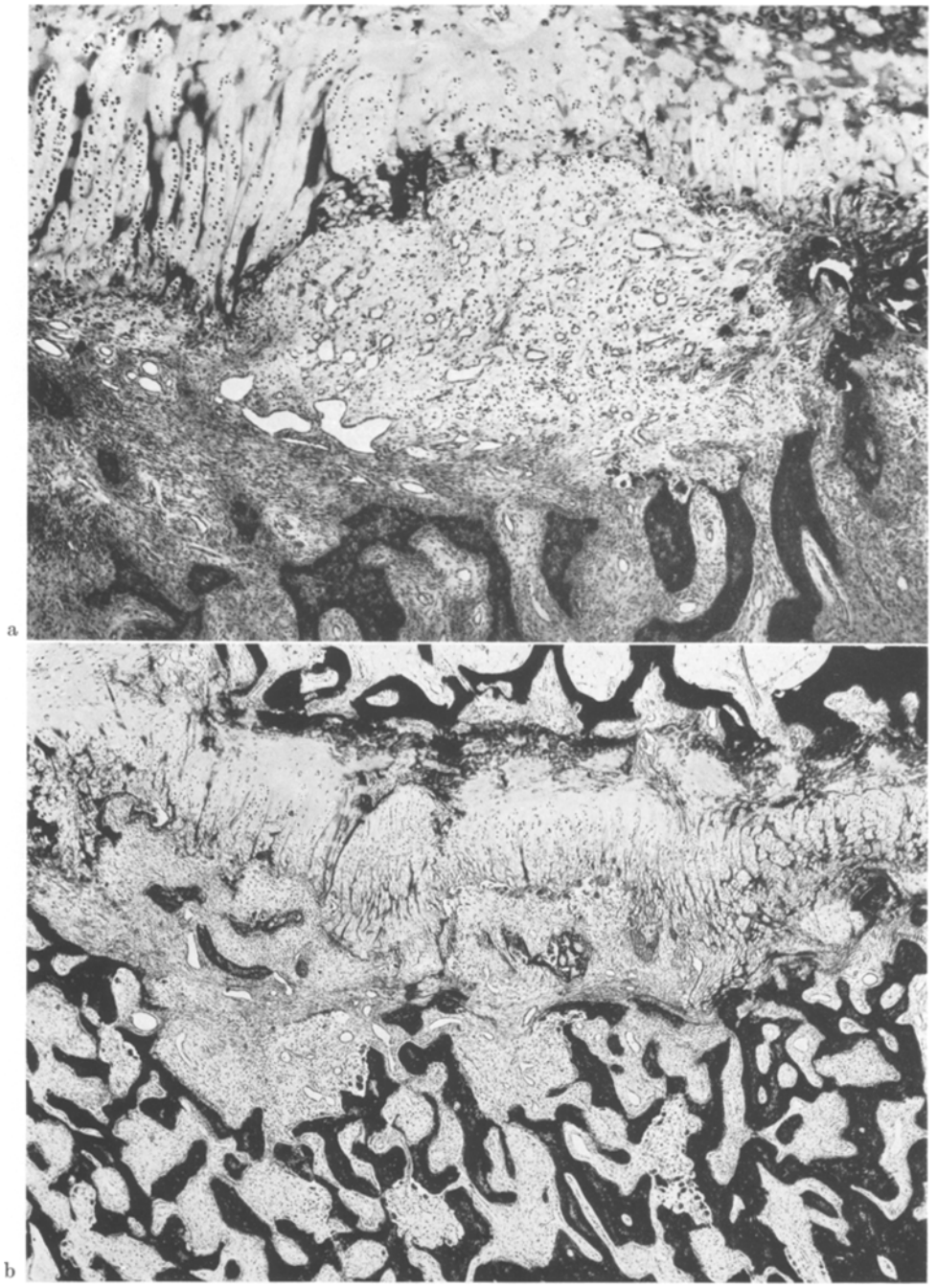


Fig. 3a and b. Detail from Fig. 1. a Large cystic cavity underneath the cartilage resulting from excessive chondroclastic activity. Dense fibrous tissue with numerous highly atypical sinusoidal vessels, no vascular invasion of the cartilage. b Small cartilage plate with irregular border towards the metaphysis. Numerous cystic excavations between cartilage and metaphysis. Lack of primary spongiosa. Deflected cartilage columnae and collagen fibers running parallel to the plane of cleavage. Microphotograph, Masson-Goldner stain, enl. a 1:40, b 1:20

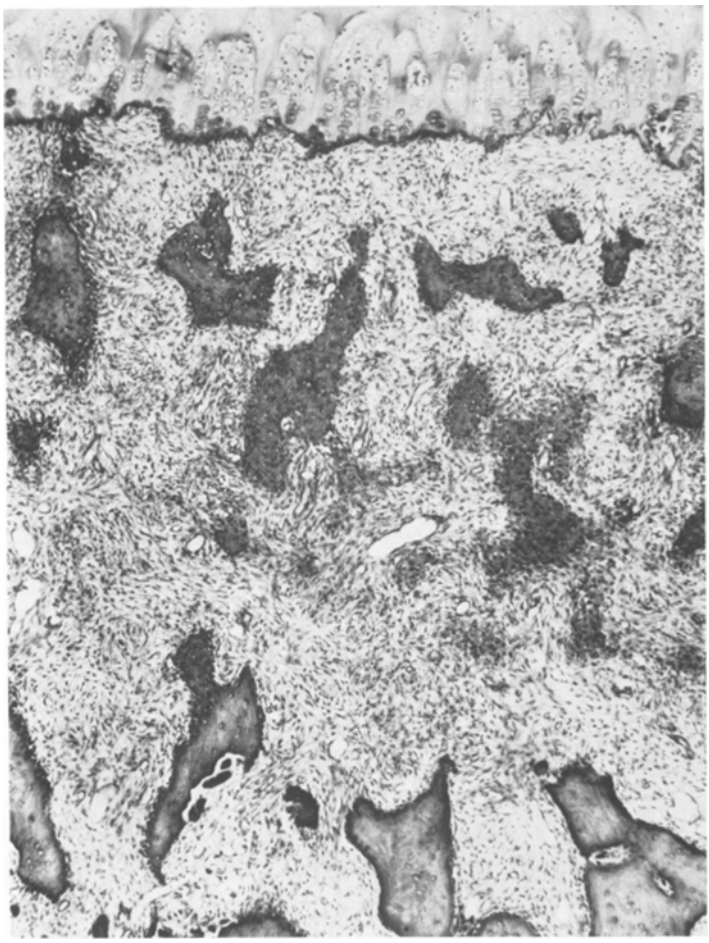


Fig. 4a and b. a Distal femur, No. 383/72. Smoothed metaphyseal border of the cartilage due to chondroclastic erosion. No vascular invasion of the cartilage. Dense fibrous tissue instead of primary spongiosa. Metaplastic formation of atypical woven bone without trajectorially orientation. b Distal femur, 12 y. old boy, No. 650/72. Beginning growth arrest with grape like cluster formation of cartilage cells. Microphotograph, Masson-Goldner stain, enl. a 1:60, b 1:125

trabeculae. Atypical trabeculae devoid of chondroid were formed metaplastically underneath the growth cartilage. The gap between the two was filled up by dense fibrous tissue. Consequently, under the influence of shearing forces, the epiphysis was moved laterally sliding along the cleavage plane of fibrous tissue using it as a slipway.

The abscence of an anatomical connection between the epiphyseal growth cartilage and the metaphysis appears to be the consequence of the following pathological processes:

1. growth arrest,

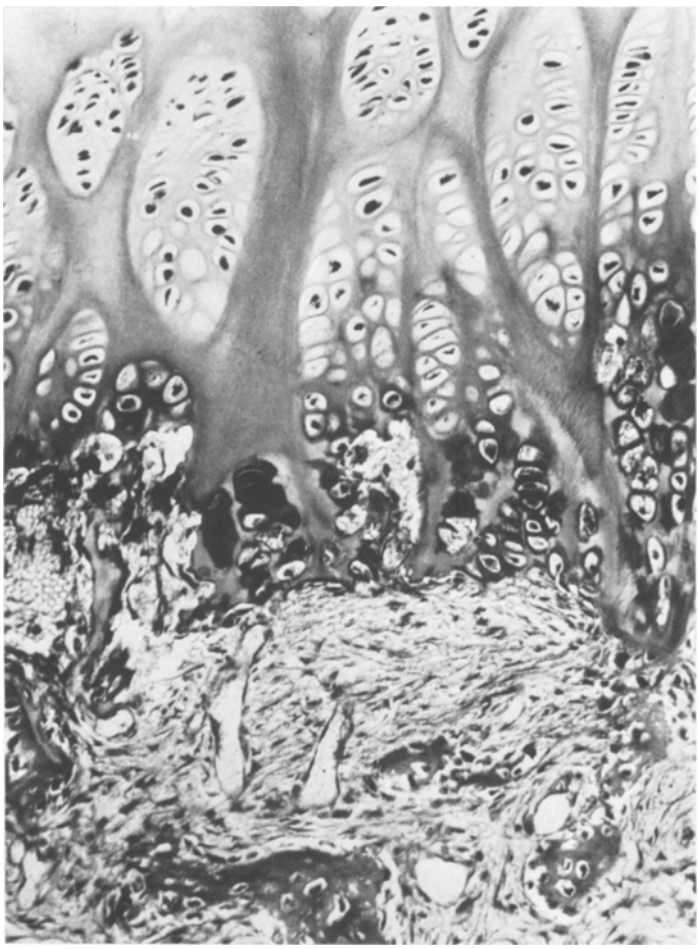


Fig. 4b

2. increased resorption of cartilage and bone and
3. disturbed vascular invasion of the growth cartilage.

Like any severe disease, uremia causes cessation of longitudinal growth. Growth arrest is known to lead to the sealing of the growth plate with a dense transverse bone plate, which normally is connected with the underlying metaphysis by a network of longitudinal trabeculae (Harris, 1933; Park, 1964; Krempien *et al.*, 1971, 1972a and b; Ritz *et al.*, 1973). In uremia intensive osteoclastic destruction on the zone of primary spongiosa was seen to have removed these supporting truts leaving the chondro-osseous complex without support. Following increaseds chondroclastic erosion of the cartilage due to secondary hyperparathyroidism, the calcified cartilage cores of the primary zone of calcification were minute or entirely absent. Finally, the regular well coordinated process of invasion of the hypertrophic cartilage by vessels is seriously disturbed in renal insufficiency. Presumably

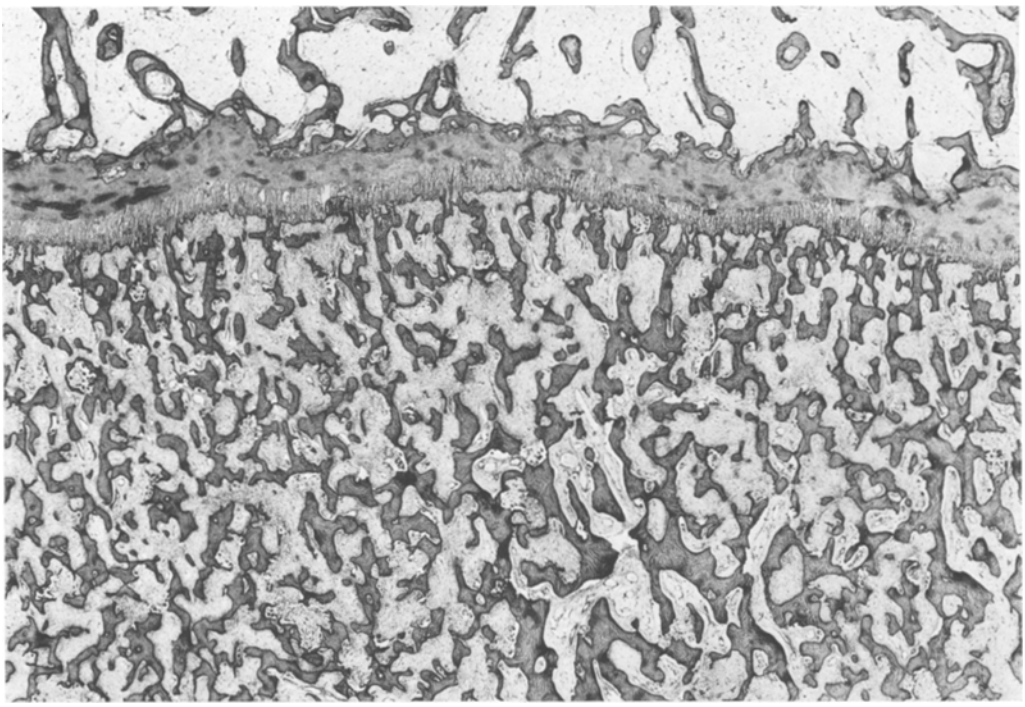


Fig. 5. No. 329/72, 5 y. old boy. Small epiphyseal plate of the distal femur. Osteosclerotic metaphysis with coarse trabeculae and dense fibrous tissue. No primary spongiosa. Microphotograph, Masson-Goldner stain, enl. 1:10

under the influence of excessive parathyroid hormone activity the vascularized mesenchymal tissue at the border region between growth cartilage and metaphyseal spongiosa is transformed into dense, poorly vascularized fibrous tissue. This substitution of a fibrous tissue for pluripotent undifferentiated tissue interrupts the ordered sequence of vascular invasion of the cartilage and deposition of osteoid by osteoblasts. Capillaries and osteoblasts can no longer be formed. Instead of capillaries coarse sinusoidal vessels are found, devoid of perithelial cells, from which normally the osteoprogenitor cells derive.

According to Pauwels (1958) bone can be laid down by osteoblasts only in the absence of mechanical irritation. Since calcified chondroid has been shown to exhibit marked mechanical stability and to offer resistance to lateral deflection, the absence of mineralized chondroid cores may well cause constant microdamage, which must necessarily interfere with the action of osteoblasts.

In conclusion the abnormalities at the epiphyseal-metaphyseal junction appear to be the consequence of defective differentiation of invading vascular tissue and of defective differentiation of osteoblasts. The loss of anatomical connection between the growth cartilage and metaphyseal spongiosa occurs by intensive chondroclastic and osteoclastic erosion and leads to the replacement of the connecting chondro-osseous structures by dense fibrous tissue. This is apparently the

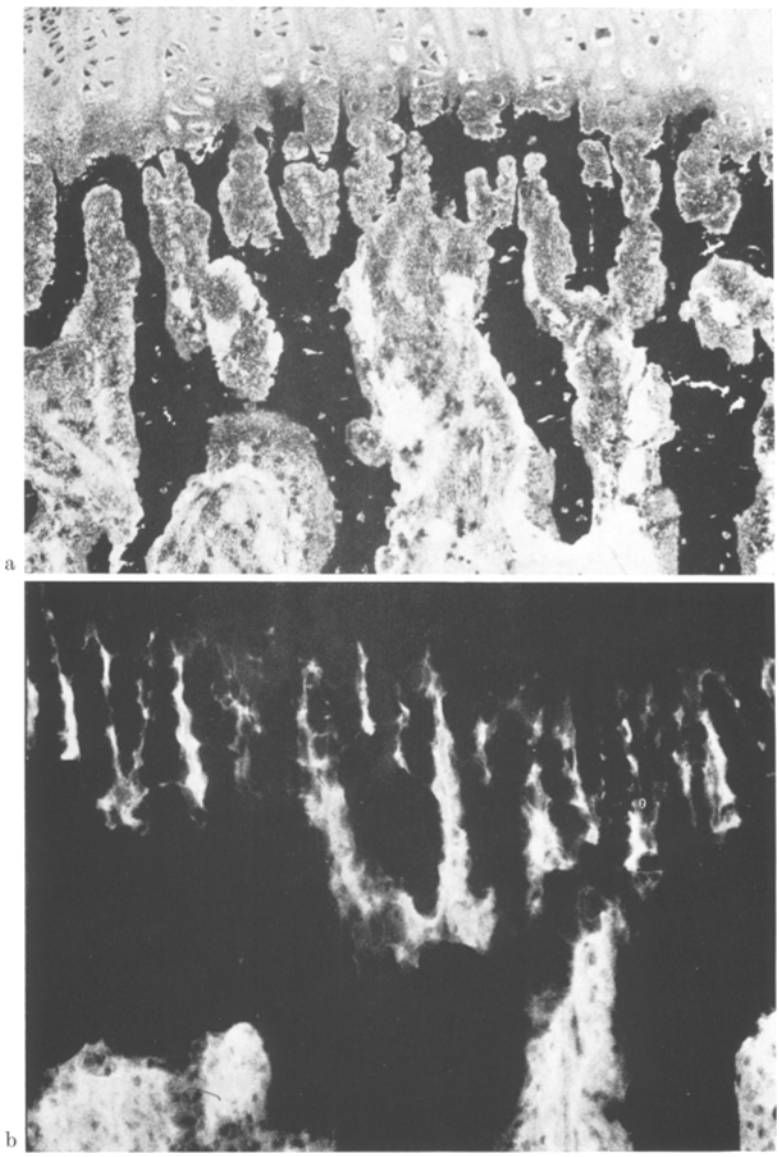


Fig. 6a—d. Zone of primary calcification in the distal femoral epiphyseal plate, a and b from a normal, c and d from a 10 y. old girl with endstage renal failure: no obvious differences. a and b Undecalcified section, von Kossa stain, enl. 1:100. c and d microradiography of undecalcified ground sections (100 μ), enl. 1:100, microphotograph

decisive process that unlocks the epiphysis and provides a slipway for lateral movement. These lesions are clearly due to parathyroid overactivity, which readily explains the clinical finding that epiphyseal slipping is only found in cases with advanced hyperparathyroidism (Mehls *et al.*, 1973). It is pertinent to mention

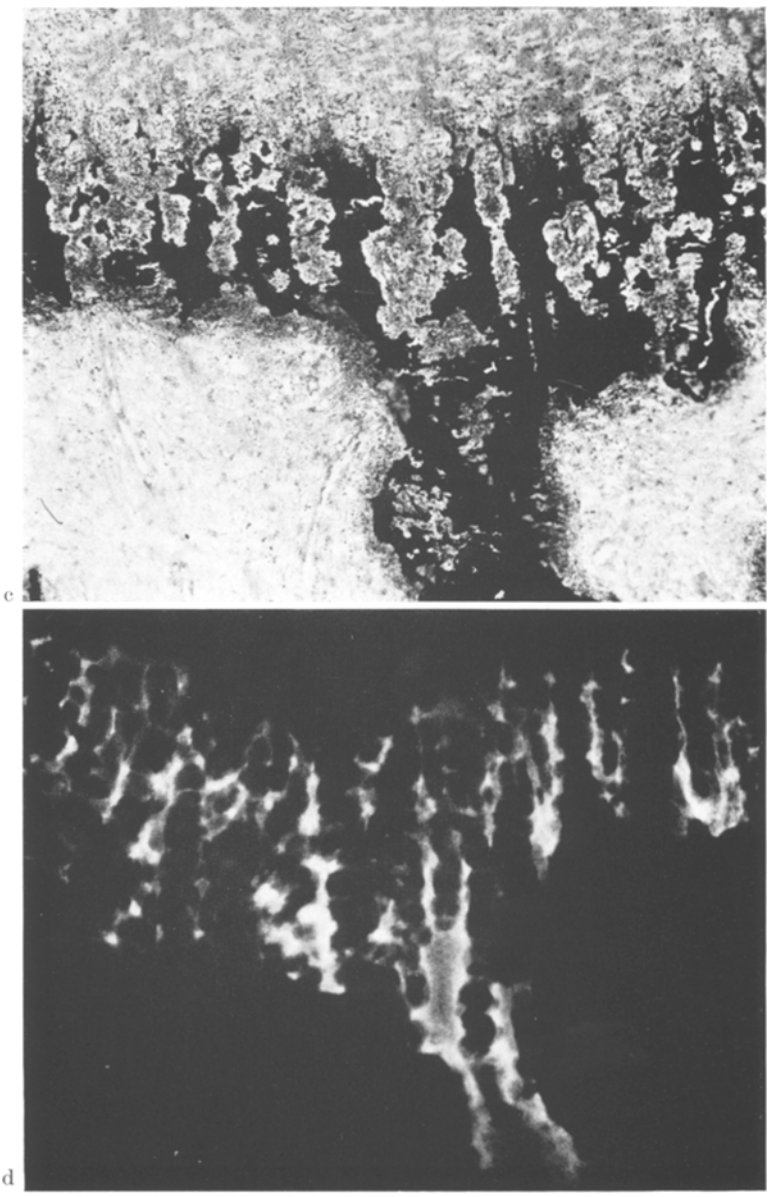


Fig. 6 c and d

that in pure vitamin D deficiency rickets epiphyseal slipping is virtually never encountered.

The abnormalities at the chondro-osseous complex are accompanied by equally important changes at the lateral metaphysis. In normal bone resorption processes reduce the perimeter of the epiphyseal flange to the diameter of the diaphyseal

shaft (so called "funneling"). In uremic patients the resorptive processes at the outer metaphysis continue after longitudinal growth has ceased. Consequently the outer part of the epiphysis is no longer supported by cortical bone and by metaphyseal trabeculae. The exaggerated deposition of undermineralized woven bone underneath the overriding cartilage plate (which is the anatomical basis of the X-ray sign of the "rotten fence post", Kirkwood *et al.*, 1972) creates additional mechanical instability. This is well documented by the occasional finding of fractures in the growth cartilage at the point where metaphyseal spongiosa changes into loose masses of woven bone.

According to Stanbury (1957) the radiological appearance of the growth apparatus in chronic renal failure can be indistinguishable from those in late nutritional rickets. Hamperl and Wallis (1933) described morphological findings in two cases of "renal rickets" with enlarged growth cartilage. However, in all cases under study typical signs of rickets (enlargement of hypertrophic cartilage with failure of calcification, cupping of metaphyses) were lacking. This may be due to arrest of longitudinal growth, which can be account for apparent healing of rachitic lesions (Stanbury, 1957). Growth arrest indeed was documented in our cases by an osseous bar between cartilage and metaphyses.

The histological evidence in idiopathic epiphyseolysis published so far is compatible with the view that the plane of cleavages is provided for by fibrous tissue within the damaged growth cartilage. The fibrous tissue presumably arises in response to continuous mechanical irritation (Sutro, 1935; Lacroix and Verbrugge, 1951; Ponseti, 1956; Taillard, 1964). While the available histological evidence does not permit to further define the primary disturbance, in idiopathic epiphyseolysis the initial lesion is clearly located in the cartilage underneath the resting zone. Uremic epiphyseolysis is distinguished from idiopathic epiphyseolysis, however, by the intensive fibroosteoclastic lesions in the primary spongiosa.

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