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Pathology of Infantile Cortical Hyperostosis (Caffey's Disease)

REPORT OF A CASE*†‡

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A few prenatal cases of infantile cortical hyperostosis, or Caffey's disease, have been reported[1,2,10,13]. Two fetuses were dead at the thirty-first and twenty-fourth weeks of gestation[2]. In two siblings, reported on by Barba and Freriks, the condition was demonstrated radiographically *in utero* during the last month of gestation. One child survived an unusually severe and protracted course, and the other recovered in a few weeks.

As a rule the disease appears in the first months of life; the clinical course is highly variable, with eventual recovery[4-6,8,16,19,21]. Only five patients are reported to have died[9,13-15,24]; in none was the cause of death related to Caffey's disease. Knowledge of the pathology has come from biopsy in nine children[7,11,19,21], radical amputation in two[7], and necropsy in four[2,9,14,15].

In this paper we report a fatal case, with classic features apparent at birth, in a child who survived for five and a half months. A postmortem study was carried out in which the humerus, tibia, fibula, ribs, vertebrae, and skull were examined by light and electron microscopy.

Case Report

This girl was born in Pavia, Italy, on February 22, 1982. In neither branch of the family was infantile cortical hyperostosis recognized. The mother was healthy throughout this first pregnancy, which was normal until the fifth month, when polyhydramnios was observed. The mother had been taking Tavor (lorazepam) and Valium (diazepam) until she became aware of the pregnancy. Placental detachment at the twenty-ninth week led to a cesarean delivery. The child, who had anoxia, was maintained by mechanical ventilation for the first five days of life. She was hypotonic, with a weak cry. The skin of all of the limbs was pigmented, and the bones were enlarged and bowed. The skull and thoracic cage were ex-

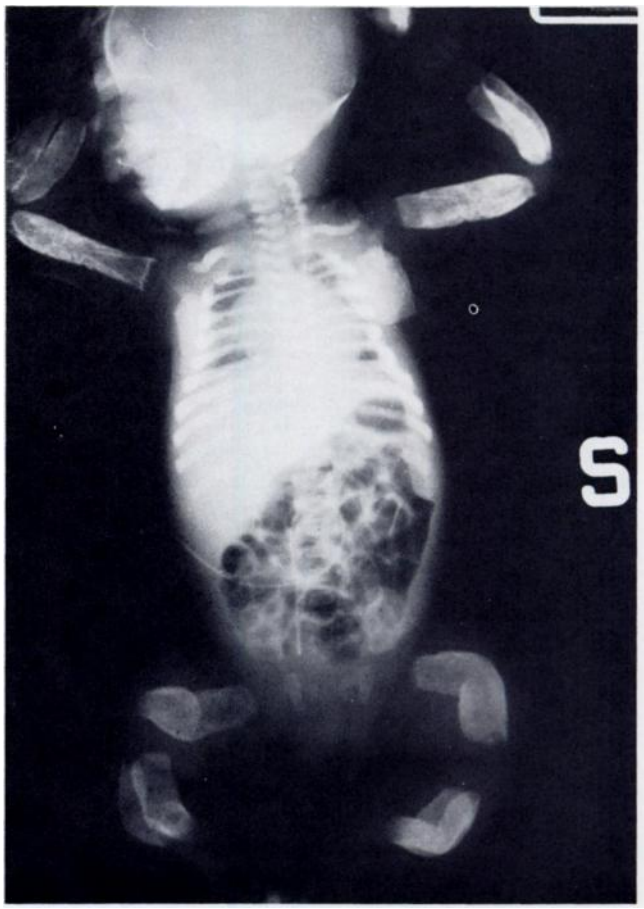

FIG. 1

Radiographic survey of the skeleton made at birth. There are extensive lesions of the long bones, ribs, left scapula, and mandible.

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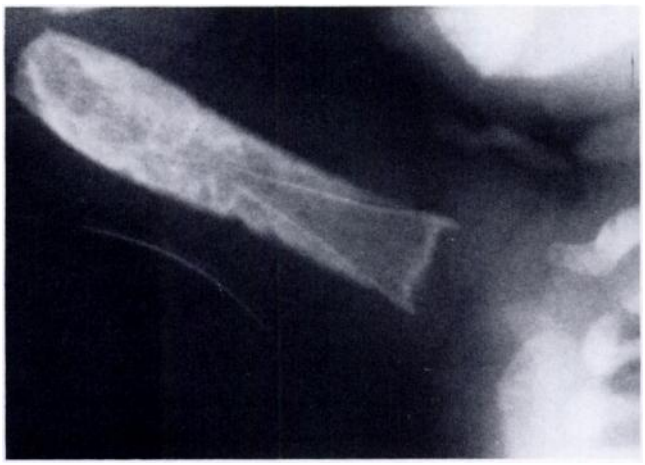

FIG. 2-A

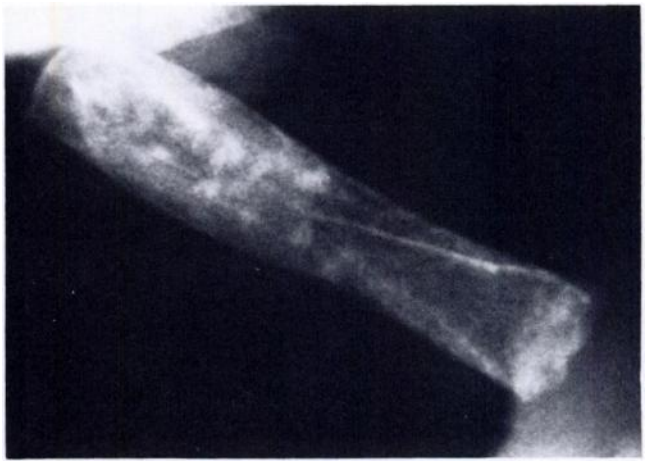

FIG. 2-B

Figs. 2-A, 2-B, and 2-C: Radiographs of the right humerus.
Fig. 2-A: At birth.
Fig. 2-B: At the age of two and one-half months. New tissue is laid down around the original cortical bone, which is progressively remodeled and resorbed.

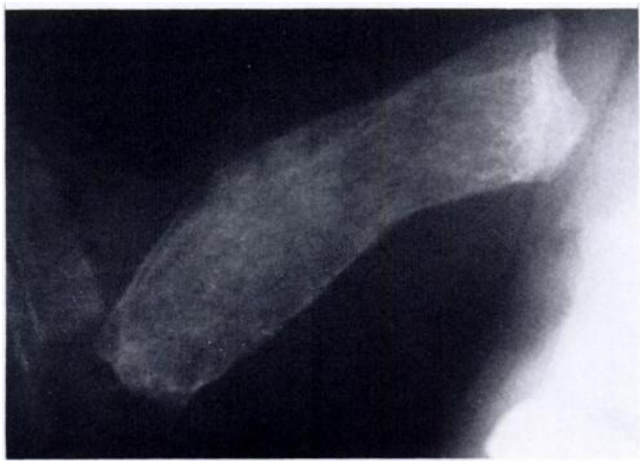

FIG. 2-C

At the age of five months, cortical bone is no longer observable.

tremely soft. The cranial sutures and fontanelles were normal, but the ribs were expanded. The illness was characterized by anemia, requiring frequent transfusions; difficult feeding, the birth weight being regained only on the forty-fifth day; episodes of urinary tract infection; respiratory difficulty; and progressively more severe bronchopulmonary infections, leading to death at the age of five and a half months.

Radiographic Observations

At birth, all of the major long bones on both sides, as well as the mandible, left scapula, and all ribs, were affected by the same abnormality: an increase in diameter through periosteal apposition (Fig. 1). In the less affected bones much of the original structure, normal in dimensions, was enclosed by the new tissue. Serial radiographs showed that the abnormal bone increased in amount and the original bone was progressively remodeled out of existence (Figs. 2-A, 2-B, and 2-C).

Both femora, tibiae, and fibulae were bowed (Fig. 3). The skull, metacarpals, phalanges of the hands, right scapula, both clavicles, vertebrae, pelvis, metatarsals, and phalanges of the feet were normal at birth. However, by the age of five months the vertebrae had collapsed.

Laboratory Findings

The following measurements and tests were carried out on one or more occasions and had normal results: Coombs' test; coagulation tests; polymorphonuclear leukocyte count; glucose; nitrogen; creatine; bilirubin; serum glutamic-oxaloacetic transaminase; serum glutamic-pyruvic transaminase; sodium chloride; potassium; calcium; magnesium; inorganic phosphate; alkaline phosphatase; parathyroid and thyroid hormones; Venereal Disease Research Laboratory test; antibodies against toxoplasma, mononucleosis, and rubella; viral cultures; bacterial blood cultures; and a karyogram.

The abnormal laboratory-test results were for anemia (despite repeated blood transfusions); immunoglobulins in the first weeks of life (IgG, 961 milligrams per 100 milliliters; IgA, thirty-two milligrams per 100 milliliters; and

TABLE I

LEVELS OF HYDROXYLYSINE GLYCOSIDES

Age (Days)	Diglycoside (mg/100 ml)	Monoglycoside (mg/100 ml)	Hydroxylysine (mg/100 ml)	Diglycoside/ Monoglycoside Ratio	Per Cent Glycosylation
24	305	164	137	1.85	77
75	282	221	365	1.27	58

IgM, seventy-two milligrams per 100 milliliters); and urinary hydroxylysine glycosides (Table I).

Necropsy

Necropsy was performed twenty hours after death. The following bones, with the periosteum, were removed: right humerus, right tibia and fibula, second through sixth thoracic vertebrae, second through sixth ribs from both sides, sternum, and right parietal bone. Radiographs of these bones were made and specimens were selected for light and electron microscopy. Those intended for study by light microscopy were fixed in neutral formalin. Some were decalcified in EDTA, embedded in paraffin, and sectioned. The stains that were used were hematoxylin and eosin, periodic acid-Schiff, and alcian blue in 0.05, 0.3, and 0.8-molar solutions of magnesium chloride, some being pretreated with bovine testicular hyaluronidase.

The undecalcified specimens were embedded in methylmethacrylate, sectioned, and stained with solochrome. For electron microscopy, specimens of epiphyseal cartilage, growth plate, periosteum, and subperiosteal calcified material were fixed in glutaraldehyde, buffered at pH 7.4, postfixed in osmium tetroxide, embedded in Epon 812 resin, sectioned, and then stained with uranyl acetate and lead citrate.

Observations

Bilateral bronchopneumonia and suppurative bronchitis were confirmed at autopsy, and signs of terminal heart failure were found.

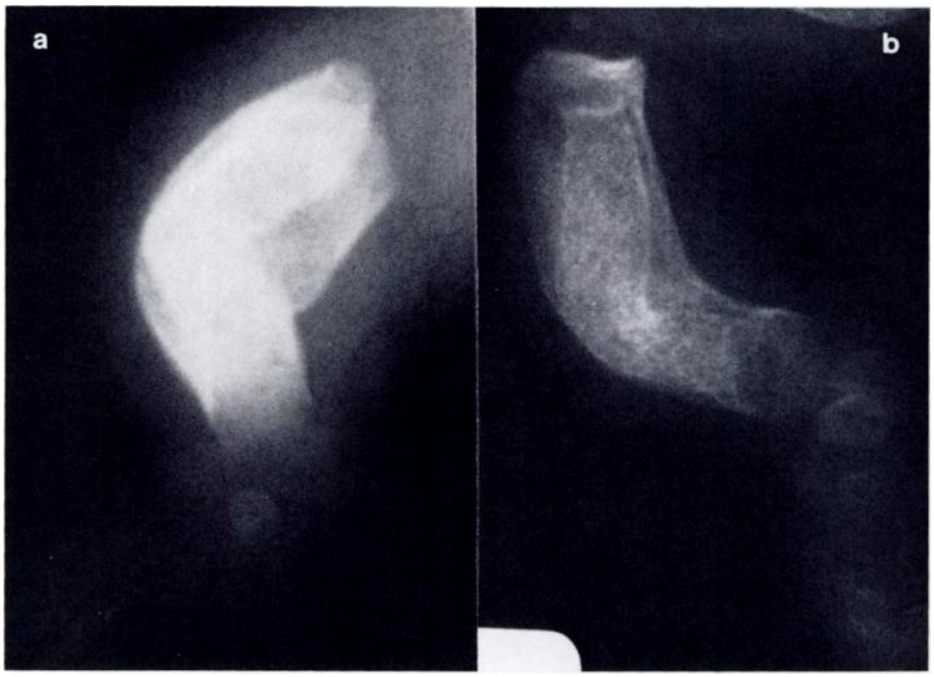

FIG. 3

Lateral radiographs of the right leg, made at birth *(a)* and at the age of five months *(b)*. The tibial and fibular diaphyses show 90 degrees of bowing.

All of the bones that were studied showed the same features, with only minor differences. The condition of the humerus will be described fully as an example, supplemented by comments on the other bones.

No cortical bone was detectable either by the naked eye or radiographically. The epiphyses were entirely cartilaginous, with a normal vascular pattern. The growth-plate organization and calcification were normal, but some columns of chondrocytes persisted into the primary ossification zone, introducing an abnormal element in the development of primary metaphyseal bone trabeculae. Nevertheless, ossification had taken place and remodeling had produced

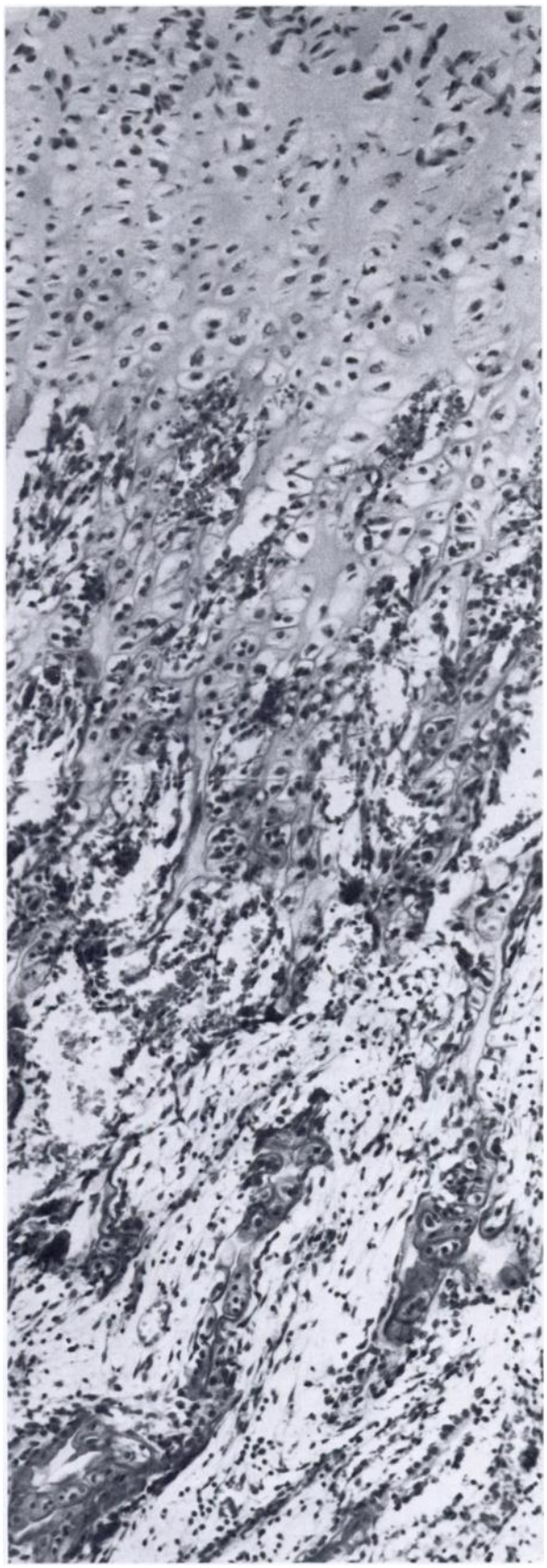

FIG. 4

Decalcified section of the right humeral growth plate and metaphysis. There is persistence of hypertrophic chondrocyte columns in primary metaphyseal trabeculae. Remodeling is carried out by osteoclasts. A richly vascular fibrous tissue with many small round lymphoid cells is present between trabeculae (hematoxylin and eosin, × 120).

trabeculae of the usual woven collagen structure. They were fully calcified, with osteoid seams of normal width. Between the trabeculae was a richly vascular fibrous tissue, infiltrated by lymphocytes (Fig. 4). Hematopoietic cells were few and aggregated in foci of active hematopoiesis.

All of the diaphyseal bone was abnormal; it was constituted by partially calcified trabeculae between which was fibrous tissue, continuous with that in the metaphysis. Scattered hematopoietic cells were present, but no other inflammatory cells. There was a marrow cavity in the middle of the diaphysis, approximately corresponding to the diaphyseal channel of a normal bone, which was filled with hematopoietic marrow (Fig. 5).

The diaphyseal trabeculae had an immature structure, with irregularly distributed large, round lacunae. There was vigorous remodeling; the extensive osteoid was mostly covered by active osteoblasts, and osteoclasts were readily identified on the resorption surfaces. Inert surfaces were few. The replacement of the original bone had been so extensive that it was only with great difficulty that definitely lamellar bone was found. It was incorporated in the new tissue (Figs. 6-A and 6-B). The fibrous periosteum was thick, with several layers of large collagen fibers running in a longitudinal, transverse, or oblique direction (Figs. 7-A and 7-B). Many vessels were present in the outer layers.

Focally, the inner surface of the periosteum was intensely cellular, with frequent mitotic sites (Figs. 8-A, 8-B, and 8-C) where slender trabeculae were being formed perpendicular to the long axis of the bone. These trabeculae are destined to develop into more substantial structures as they come to lie beneath later additions. Elsewhere, subperiosteal bone resorption was active (Fig. 9). The distribution pattern of periosteal activities was clearly determining the shape of the bone.

In the tibia (Fig. 10) there was no trace at all of the diaphyseal channel. The costochondral cartilage had the same irregularity as did the humeral growth plate. No trace of diploë was observed in the calvarium, whose structure, uniform throughout, was of the same stout immature trabeculae as elsewhere. The vertebrae were reduced in height and, again, had the same irregularities in the growth plate. The marrow space was mainly fibrous, but there were residual areas of hematopoiesis.

The periodic acid-Schiff and alcian-blue preparations showed a normal matrix in the epiphyseal and growth-plate cartilage. Ultrastructurally non-specific degenerative changes were present in epiphyseal cells. However, the cells of the physis were better preserved and a normal pattern of maturation was present, with mucopolysaccharide precursors in large cisternae in cells of the proliferative layer. An unusual feature was the presence of a paranuclear lipidic droplet in many cells (Fig. 11). Hydroxyapatite crystal deposition was normal.

The outer periosteal layer was composed almost entirely of densely packed, normal collagen fibrils. The remaining fibers, rather less than 1 per cent, were abnormal, irregularly distributed, large, aperiodic, and composed of parallel filaments (Fig. 12). Their appearance suggested that

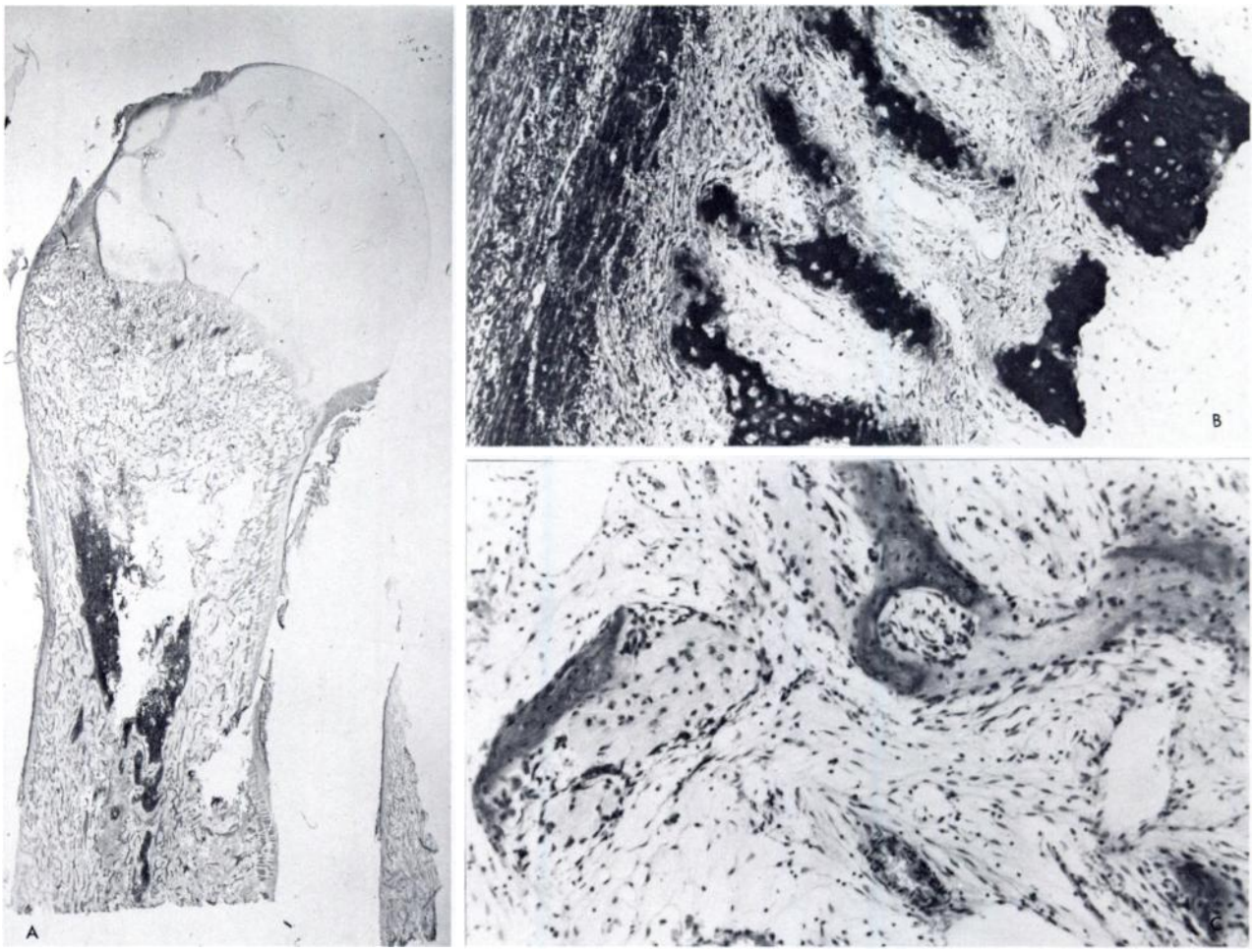

FIG. 5

The right humeral diaphysis. *A*, Decalcified longitudinal section of the humerus. No cortical bone is observed, and the diaphysis is entirely constituted of cancellous bone. Bone-marrow tissue is present in the middle of the diaphysis (hematoxylin and eosin, × 2.5). *B*, Undecalcified section showing subperiosteal formation of partially calcified bone trabeculae (solochrome, × 100). *C*, Decalcified section showing cancellous bone of the diaphysis and fibrous tissue with lymphoid cells between trabeculae (hematoxylin and eosin, × 100).

they were elastic fibrils, but this could not be confirmed.

An incomplete initial phase of calcification of the periosteal osteoid conformed with the high rate of bone-remodeling, as did the large osteocyte lacunae with their irregular perilacunar uncalcified matrix.

Discussion

The diagnosis in this case lies between infantile cortical

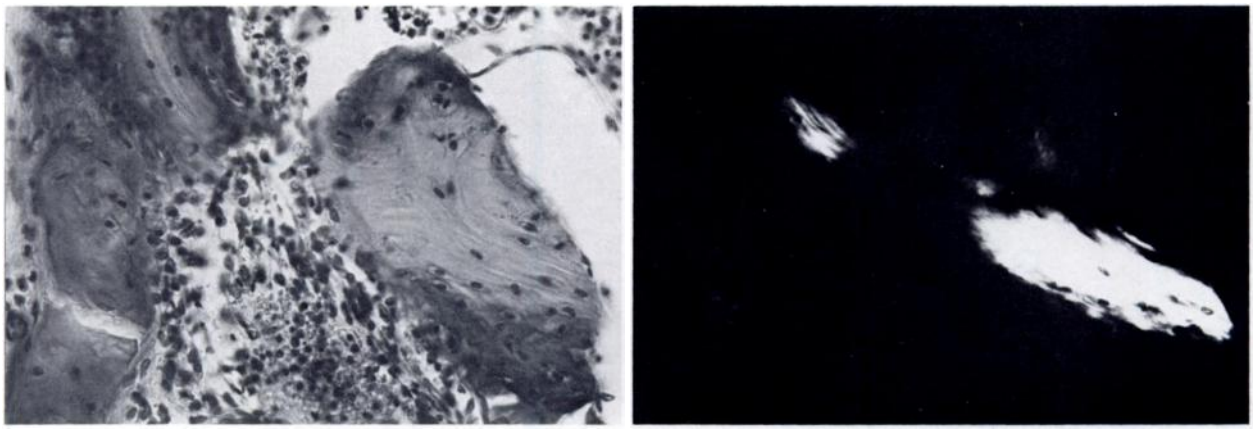

FIG. 6-A FIG. 6-B

Figs. 6-A and 6-B: Decalcified section of the right humerus (hematoxylin and eosin, × 400).
Fig. 6-A: Residual lamellar bone is incorporated in the new immature bone.
Fig. 6-B: The same field viewed under polarized light.

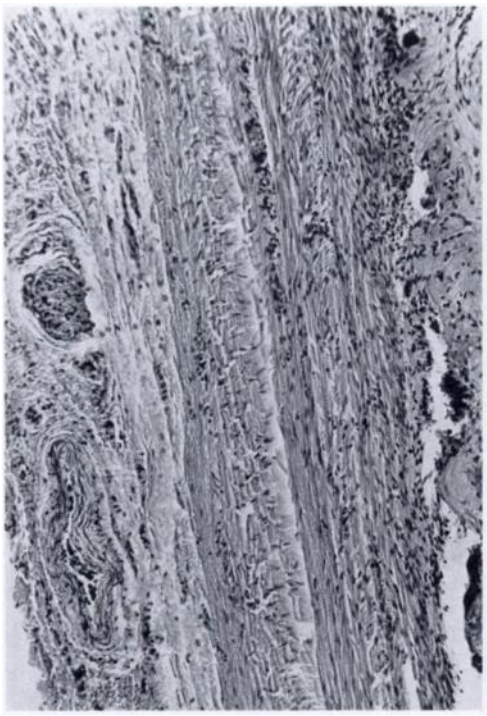

FIG. 7-A

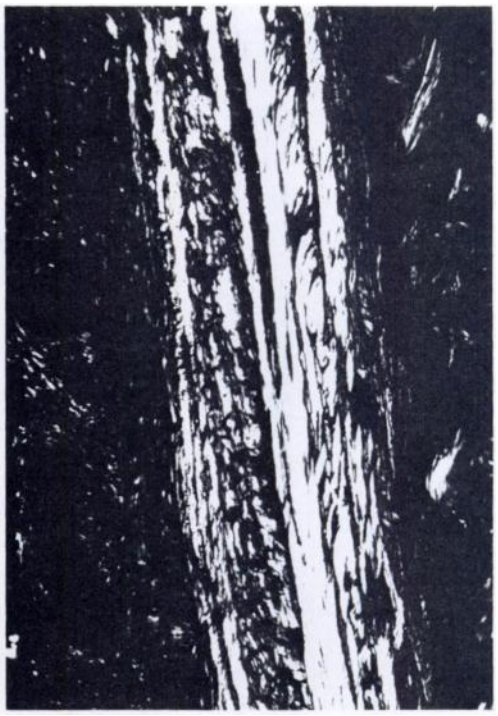

FIG. 7-B

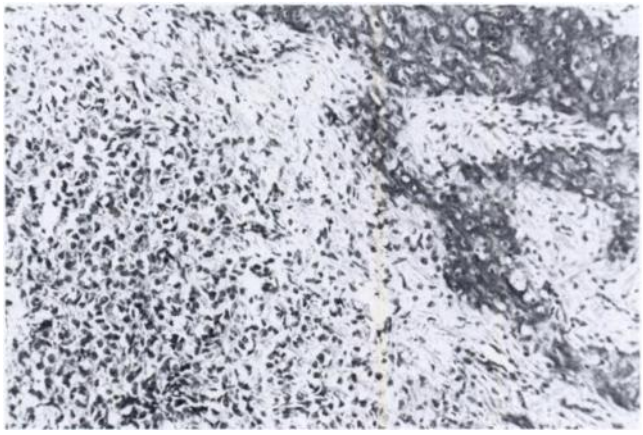

FIG. 8-A

FIG. 8-B

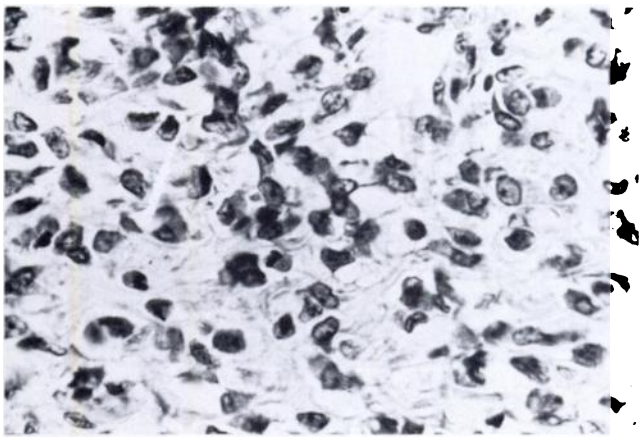

FIG. 8-C

hyperostosis and osteogenesis imperfecta. Factors that argue against the latter are the involvement of the mandible, the absence of a hereditary component, the lack of other signs such as blue sclerae and delicate skin, the failure of the original cortical tissue to persist, and, most important of all, the total absence of fractures. From the time of recognition of the infant's illness at birth, this feature was looked for. Although bowing of long bones was present, it was clearly tense proliferation of subperiosteal cells, which, in two patients was misdiagnosed as malignant disease and led to amputation[7]; subperiosteal new-bone formation; and fibrosis of bone marrow. Nevertheless, some unusual features were present: onset *in utero* (only two cases previously reported); generalized bone lesions, including the skull and the vertebrae (features not previously reported); and a fatal outcome (only five cases previously reported). The etiology is un-

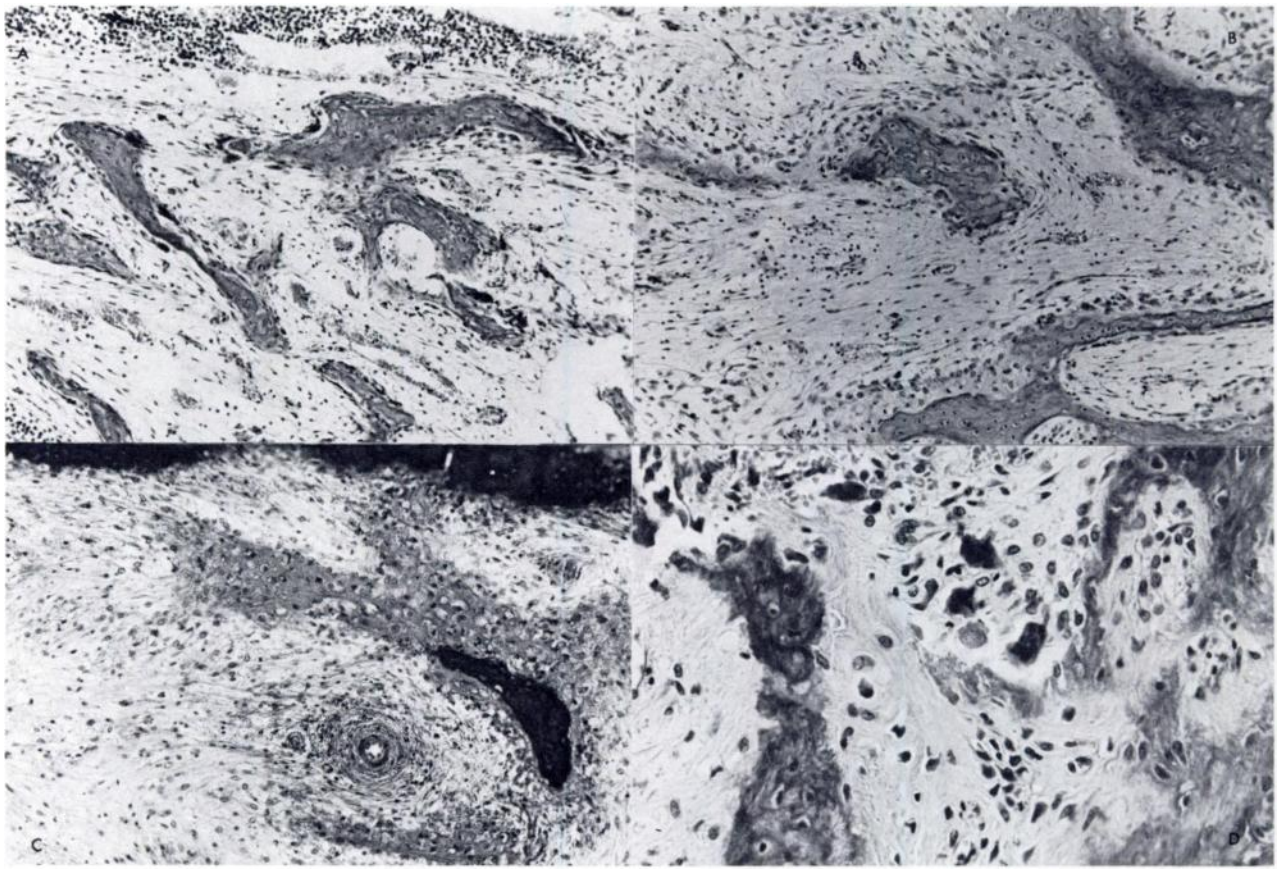

FIG. 9

Remodeling of immature bone trabeculae in the right humerus. *A*, Osteoclasts are resorbing immature bone trabeculae (decalcified section, hematoxylin and eosin, × 100). *B*, Osteoblasts line the surface of trabeculae, and medullary fibrosis is also evident (decalcified section, hematoxylin and eosin, × 100). *C*, Note the wide osteoid border of immature bone trabeculae (undecalcified section, solochrome, × 100). *D*, Immature bone trabeculae and osteoclasts (decalcified section, hematoxylin and eosin, × 400).

a manifestation of periosteal remodeling, and could not be satisfactorily imputed to intrauterine fracture. The child was sufficiently active, and had to be handled to a degree that would certainly have resulted in fractures in a patient with osteogenesis imperfecta of this severity. The histopathological observations were the same as those in previous biopsy and necropsy reports, and may be summarized as follows: thickening of the periosteum; absence of cortical bone; inknown but, given the pathogenetic mechanism of increased periosteal growth and diffuse diaphyseal remodeling of affected bones, the possibilities can be narrowed down to genetic, inflammatory, and metabolic causes. The last of these is not supported by the extensive evidence from reported cases or by the many investigations of this patient, and will not be considered further. The first is suggested by the appearance of disease in siblings[1,3,20,24] and in

Figs. 7-A and 7-B: Decalcified section of the right humerus (hematoxylin and eosin, × 100).
Fig. 7-A: The periosteum is thickened, with multiple layers of collagen fibers and vessels on the outer surface.
Fig. 7-B: The same field under polarized light.
Figs. 8-A, 8-B, and 8-C: Decalcified section of the right humerus.
Fig. 8-A: There is intense subperiosteal cellular proliferation (hematoxylin and eosin, × 100).
Fig. 8-B: The same field as Fig. 8-A, under polarized light.
Fig. 8-C: Detail of Fig. 8-A. Cellular mitoses are often observed (hematoxylin and eosin, × 400).

families[12,18,20,22]. Opposed to this is the natural course of the disease in the majority of patients — onset, progression, and recovery without sequelae — which is best accounted for by an inflammatory pathogenesis. Moreover, several features of the case of our patient do not fit in with the genetic hypothesis: epiphyseal and metaphyseal development was found to be normal; the main site of pathogenetic activity was diaphyseal periosteal activity and cortical remodeling; and the initial development of the long bones does not refute the hypothesis. The example of Paget's disease of bone usefully illustrates this. In addition, the disease started *in utero*, when the infant was not under observation. Moreover, in biopsy specimens taken early in the course of the disease in other patients, the presence of inflammation has been established[7]. Support for the hypothesis of an inflammatory etiology due to infection in this patient rests on the increased concentrations of plasma IgA and IgM, which were determined in the first week of life.

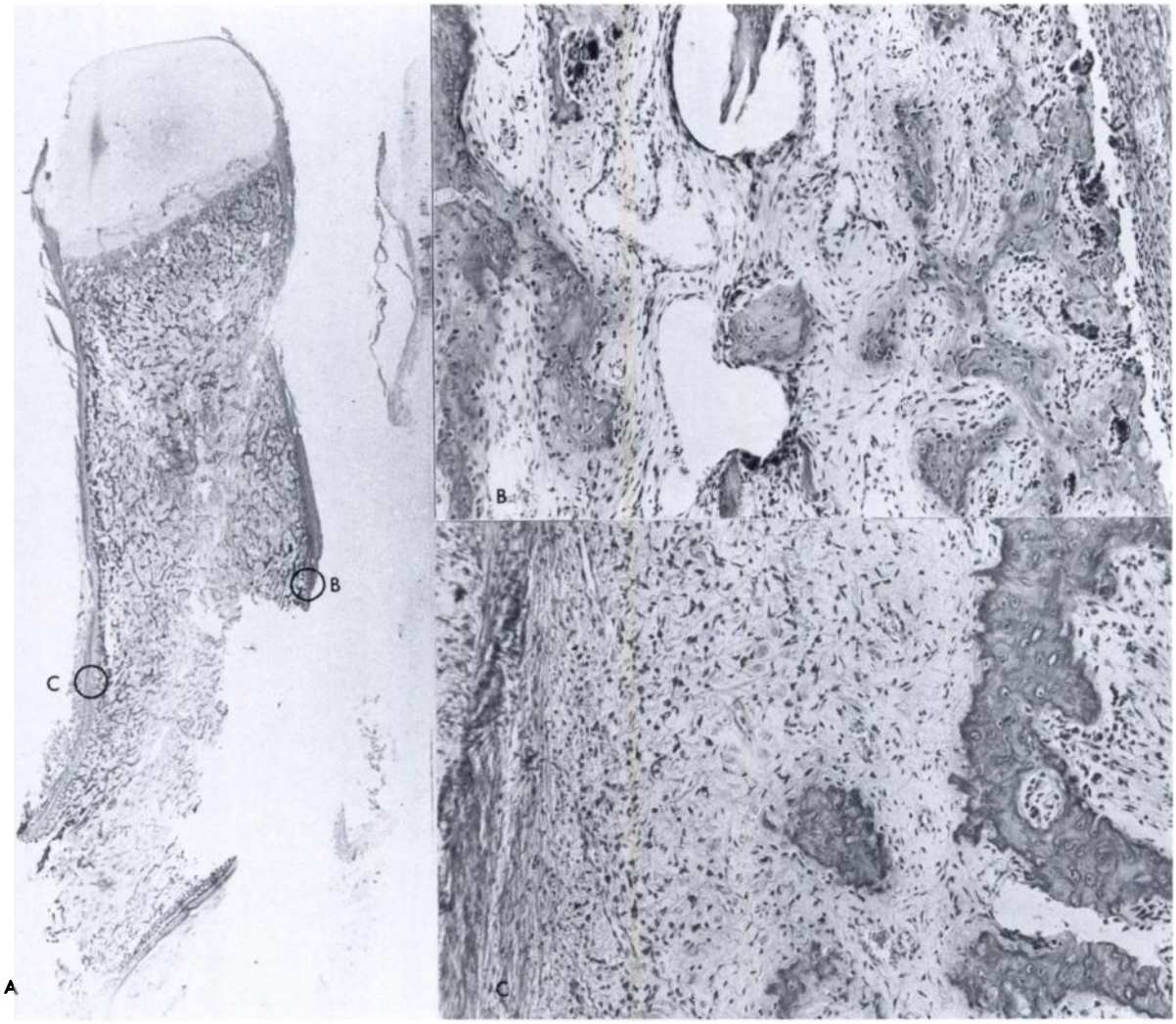

FIG. 10

Decalcified sections of the right tibia. *A*, Section in the sagittal plane (hematoxylin and eosin, × 2.5). *B*, Subperiosteal osteoclastic resorption on the convex side (hematoxylin and eosin, × 100). *C*, Pronounced osteoblastic activity on the concave side (hematoxylin and eosin, × 100).

must have been normal, as evidenced by the presence on radiographs, made at birth, of cortex in the humerus and by residual lamellar bone identifiable post mortem.

Bone is capable only of a limited type of response, which consists of turnover and remodeling. The rate and duration of its two components, resorption and formation, can vary widely, so that end results may differ in degree, but not in kind. The absence of any sign of osseous inflammation, either clinically or pathologically, in this patient, They point to stimulation of immunity before birth. Raised levels of immunoglobulins have been reported in two other cases[17,23]. The immunoglobulin determinations were not repeated because of the many blood and plasma transfusions, necessitated by the persistent anemia, which in turn was caused by widespread myelofibrosis. Although many clues observed in this and other reported cases suggest an inflammatory pathogenesis and infective etiology, no definitive evidence has so far been produced. Perhaps this is because

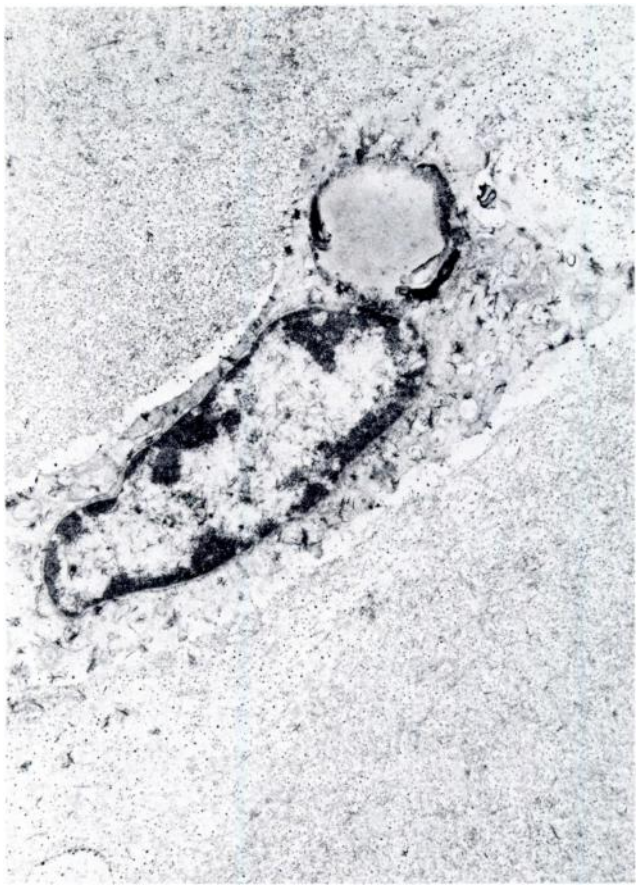

FIG. 11

Undecalcified section of the humeral growth plate. The cytoplasm of a hypertrophic chondrocyte contains a lipid droplet and clusters of hydroxyapatite crystals (× 12,600).

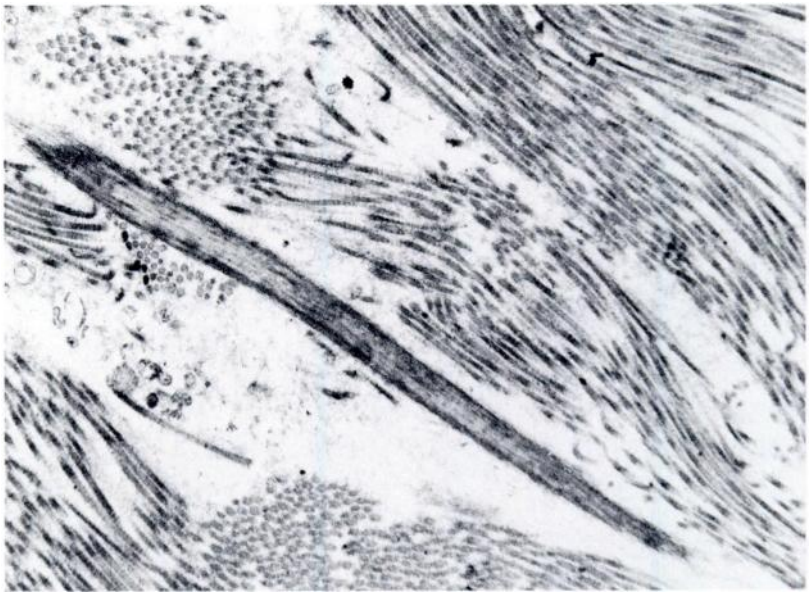

FIG. 12

Decalcified section of the diaphyseal periosteum of the humerus. The periosteum is formed by densely packed bundles of collagen fibrils, among them large fibrils without periodicity (× 21,000).

we are studying only the expression of the bone's reaction to the primary injury, which occurs *in utero*. The dictum offered by Caffey is reinforced: only study of the mother will reveal the etiology of this disease.

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