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# Pediatric Osteomyelitis and Septic Arthritis: The Pathology of Neonatal Disease

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The morphologic and histologic examination of over fifty-five foci of metaphyseal/epiphyseal osteomyelitis and eleven septic joints from five cases of neonatal osteomyelitis and joint sepsis are described in detail. The severity of the bone and joint involvement varied considerably, allowing a better understanding of the pathophysiologic sequence of events in the disease in the neonatal time period. Of particular importance were (1) the multifocal nature of the disease, (2) the highly variable destruction of the growth plate (physis) by several discrete mechanisms, and (3) the invasion of the chondroepiphysis through the cartilage canal systems. Two of the cases died from respiratory complications several months following presumed successful treatment of their skeletal infections. Specimens showed significant growth plate damage continuing beyond the neonatal period. These findings support the need for rapid diagnosis and drainage, whenever feasible, to prevent long-term skeletal growth damage. The severity of involvement also should emphasize that this disease, especially in the neonate, is not an innocuous condition, as a recent review suggested.

Classification of a specific, infantile pattern of acute hematogenous osteomyelitis has been suggested by several authors [1-8]. Trueta [9,10] discerned three different, age-related pathologic stages—infant, child, and adolescent—each with relatively specific patterns of clinical/pathophysiologic presentations of the osteomyelitis. He attributed the variability of the pathophysiology to differences in the circulatory patterns, although he had *no* corroborating specimens of osteomyelitis to support these concepts.

Within the infancy group it is becoming increasingly apparent that the neonatal period may be one of particular susceptibility to osteomyelitis. Significant predisposing factors in the first few weeks of life appear to be the changing patterns of immune status and response, the highly vascular and actively remodeling chondro-osseous skeleton, and the increasing exposure to bacteria in the extrauterine milieu. The primary causal microorganisms differ somewhat from the overwhelming predominance of Staphylococcus throughout most of childhood skeletal infection, with Streptococcus being more common [11,12]. Fungal infections also may occur [13]. Standard techniques of care during the perinatal period may cause increased risk; fetal monitoring, heel puncture, umbilical catheterization, and femoral veni- or arteriopuncture may cause chondro-osseous infection either by direct innoculation or hematogenous spread [14-18]. In this particular study, all the infectious foci grew



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*Staphylococcus aureus* on culture. Gram-negative organisms were subsequently cultured in two patients, but from the blood or tracheostomy, and not from the skeletal foci.

Recently the specific clinical nature of neonatal osteomyelitis was described [19]. Among the significant findings were: (a) multiple bone involvement, (b) joint involvement, and (c) subsequent skeletal deformity, with the latter implying significant damage to the capacity for longitudinal growth. Additional authors also have described subsequent growth deformities [5,20–29], while others have described gradual correction, or even eventual disappearance, of the initial epiphyseal and metaphyseal defects [30–33]. These descriptions of bone and cartilage destruction and subsequent angular or decreased longitudinal growth deformities, or spontaneous correction thereof, imply injury (possibly partially or completely reversible) to the growth plate (physis).

Yet Siffert [34] stated that direct bacterial invasion of the physis from a metaphyseal focus was extremely rare. Some authors have more emphatically stated that the growth plate is an absolute barrier to infectious spread [21,35–37]. In contrast, others, including the author, have observed older children with very obvious abscess continuity from the metaphysis across the physis into the epiphysis, with occasional further extension into the joint [23,38–41].

Lack of an adequate appreciation of the pathobiology of neonatal osteomyelitis can lead to misconceptions regarding the potential destructiveness of this disease, particularly when it is multifocal. Recently Fox and Sprunt [42] reviewed forty-two cases of neonatal osteomyelitis, only twenty-two of whom had long bone and/or joint infection. They implied that residual deformity was most common in those having surgical incision and drainage, although they did not define the extent of drainage or the time of surgery relative to disease onset. They felt nothing in their data could suggest that the trend toward minimal surgical intervention was harmful. However, it is unfair to suggest that surgical drainage necessarily caused the osseous growth problems, and it is equally unfair to suggest that the sixty-eight percent incidence of physeal and articular damage they reported is acceptable [43]. The current study will show the amount of chondro-osseous destruction that may occur rapidly in this age group and will emphasize the need for surgical decompression of the chondro- and osteolytic purulent material.

Trueta [9,10,29], and Ogden [44,45] have suggested that the presence of transphyseal blood vessels connecting the epiphyseal vessels with the metaphyseal sinusoids might allow passage of bacteria across the growth plate from the usual metaphyseal focus into the epiphysis. These transphyseal vessels appear to be present in many long bones during infancy, but disappear with subsequent skeletal growth. In the human most seem to disappear by eighteen months of age, although this varies from bone to bone and seems to be related primarily to the appearance of the secondary ossification center [46–49]. In many larger mammals, such as the elephant and whale, these transphyseal vessels are present throughout skeletal development [50].

The relationship between infantile proximal femoral osteomyelitis and septic hip joint is well documented [22,24,26,28,51–54], but coexistence of these two processes in other developing joints is rarely described. Yet the nuances of neonatal anatomy are such that portions of other epiphyses besides the proximal femur are intra-articular [48,49], which would explain the tendency to multiple foci of contiguous osteomyelitis and septic arthritis. Further, growth deformities, especially those involving the proximal femur in cases of septic hip, are usually attributed directly to the pyogenic arthritis, and rarely to possible physeal destruction from the osteomyeli-

tis. The role of vascular ischemia, particularly through damage to the intrinsic cartilage canal system, has not been described.

The major problem in discussing osteomyelitis in infants or children is the dearth of pathologic material. Jaffe [39] showed cases from a thirteen-year-old and a two-and-one-half-year-old. The specimen from the thirteen-year-old had metaphyseal and epiphyseal involvement, but there was no description of a communication across the physis and no histologic study. The specimen from the two-and-one-half-year-old, demonstrated histologically, had an intact growth plate and only metaphyseal involvement. To the best of the author's knowledge, no complete pathologic specimens of infantile osteomyelitis have been described.

This study will present the gross and histopathologic findings in five cases of neonatal sepsis, osteomyelitis, and septic arthritis. The important findings were: (a) multiple bone involvement; (b) multiple joint sepsis, always in association with, and seemingly *secondary to* an osteomyelitic focus; (c) highly varied destruction of the growth plate; (d) epiphyseal cartilage destruction with significant metachromatic changes in the intracellular matrix in some of the epiphyses; (e) variable occlusion of arteries, veins, and capillaries within the cartilage canal systems; and (f) an important role for transphyseal vessels in allowing spread of infection from the metaphysis into the epiphysis.

## CASE REPORTS

Pathologic specimens from five children were available for detailed examination. Four cases developed septicemia and subsequent diffuse osteomyelitis and septic arthritis within a few days of birth. In each a hematogenous route seemed most likely. The fifth case sustained a severe burn of the fingers and subsequently developed a suppurative, unifocal osteomyelitis necessitating amputation. While the focus of infection was the nearby distal radial metaphysis, presumably the microorganisms from the burn infection spread by a vascular or lymphatic route, since there was no direct connection with the burn and the osteomyelitis initially (although progressive soft tissue destruction subsequently led to continuity of these processes).

Case one will be presented in detail, first because it was representative of the usual clinical presentation and course, and second, because the entire postcranial skeleton was made available for detailed study. Brief case histories of the other four patients also will be presented.

### *Case 1*

This 3,200-gram male infant was born following an uncomplicated pregnancy, labor, and delivery. However, because of an apparent gastrointestinal obstruction and failure to pass meconium by the third day of life he was transferred to Yale–New Haven Hospital. Prior to transfer, an umbilical artery catheter had been inserted. A barium enema successfully relieved the meconium ilius. A sweat test established a diagnosis of cystic fibrosis. Hematologic studies were normal for a full-term infant. One week after transfer (ten days of age) a fluctuant mass appeared over the xiphoid region. The purulent drainage from this site, the umbilical catheter tip, and blood cultures all grew *Staphylococcus aureus.* Intravenous oxacillin at a dose of 200 mg/kg/d was administered. No other obvious sites of infection were discerned, and the child had active motion in all limbs. Over the next 72 hours, severe edema developed, and the antibiotic was changed to potassium nafcillin at a dosage of 200 mg/kg/d. This dosage gave serum bacteriocidal levels of 1/128 at thirty minutes and 1/32 at 3½ hours following drug administration. A week after inception of antibiotic

treatment, because of the development of further soft tissue abscesses and limitation of motion of multiple joints, roentgenograms were taken. These revealed no obvious skeletal lesions. His condition worsened, despite abscess drainage where possible, and the continuation of antibiotics. The purulent material repeatedly grew *Staphylococcus aureus* sensitive to nafcillin. Repeat skeletal roentgenograms five days after the previous films showed multifocal metaphyseal osteoseal osteolysis (Fig. 1). The infant developed progressive pneumonia and respiratory difficulty and died on the twenty-seventh day of life. Post-mortem examination showed pleuritis, pneumonitis with abscess formation, peritonitis, hepatic abscess, hepatic failure, and congestive heart failure. Besides Staphylococcus the post-mortem cultures were positive for Klebsiella. The entire postcranial skeleton was obtained for detailed study.

*Case 2*

This 2,800-gram male infant was born two weeks prior to anticipated delivery, the delivery having been induced because of the development of septicemia in the mother. At birth, the child was in severe distress. The child survived for four days, during which time he received sodium oxacillin. Blood cultures from the child, as well as the maternal uterus, grew Staphylococcus. At the time of death, the child had no grossly obvious infection in the extremities, although there was minimal inflammation at the hips. Pathologic examination was limited to thoracic and abdominal cavities, spine, and hips.

*Case 3*

This 3,100-gram male was the product of an unremarkable pregnancy and delivery. He was healthy until three weeks of age, when severe diarrhea developed. Three days later he was transferred to Yale–New Haven Hospital, having had two presumed septicemic episodes. A periumbilical abscess was present and two days later a subphrenic abscess was diagnosed and drained. Both infections were caused by *Staphylococcus aureus*. He was started on intravenous oxacillin. Over the next four days, he subsequently developed multifocal osteomyelitis and septic arthritis of both hips, left knee, right ankle, left shoulder, and both wrists. Roentgenographically lytic destruction was evident in all the aforementioned areas. Each abscess was surgically incised and drained. Surgical observations revealed considerable chondrolytic and osteolytic destruction in the hips, but much less damage in the shoulder, knee, and ankle. One wrist and distal radius were severely damaged. Despite six days of intravenous oxacillin *prior to* the surgery, all areas had positive cultures for *Staphylococcus aureus*. He received six more weeks of intravenous antibiotics and was discharged. His post-hospitalization course showed roentgenographic improvement at the knees, shoulder, and ankle. However, the more severely involved wrist and both hips exhibited significant growth deformation. Clinically, there was no evidence of active disease. The radiographic changes continued to worsen until sixteen months of age, when he began having respiratory difficulty from his chronic tracheostomy stoma. Shortly thereafter he was found dead at home. Only a limited autopsy was done. Portions of one hip (primarily the remaining greater trochanter) and two vertebral bodies were available for study.

*Case 4*

This 2,200-gram premature (33-week) male was admitted to the newborn special care unit with respiratory distress syndrome. He developed jaundice and required exchange transfusion. At three days of age he became septic. A CSF tap was positive

for *Staphyloccus aureus* and he was started on oxacillin. Repeat CSF tap six days later was negative. After two more days a cutaneous abscess developed over the lower sternum. This was drained and culture revealed Staphylococcus again. Over the following three days he developed abscesses of the hips, left shoulder, right knee, and right wrist. His moribund condition precluded formal drainiage in the operating room, so all areas were drained through small stab incisions. Intravenous oxacillin was continued for six weeks. All areas responded within twenty-four hours to abscess decompression, and there were no clinically evident recurrences of abscess formation during the subsequent hospitalization. After discharge, he appeared to be making a reasonable recovery, although there were areas of chondro-osseous deformity in all the osteomyelitis sites. At the age of five months he was found dead at home. He had experienced several apneic spells in the first two weeks of life, but none during the remainder of the hospitalization. He was taken to another hospital where a limited autopsy was done. A portion of the proximal femur and proximal humerus were obtained for detailed study.

*Case 5*

This infant male was brought to the Hôpital Albert Schweitzer (Haiti) at approximately four weeks of age. The forearm and hand had been burned. The fingers were charred and grossly infected, but the carpus and forearm only had second- and third-degree burns evident initially, There was an area of fluctuance over the distal radius. This was drained, but only subperiosteally. Cultures were positive for *Staphylococcus aureus* and he was started on intravenous penicillin, to which the microorganism was susceptible (chloramphenicol was the only other antibiotic available). Unfortunately, further ischemic and infectious tissue destruction, primarily a result of deeper tissue damage from the burn, continued and necessitated amputation. The distal radial and ulnar segments were sent to the Skeletal Development Study Unit at Yale for further processing.

## RESULTS

The complete post-cranial skeleton from Case 1 was available for detailed study and will be the primary one illustrated (Figs. 1–14). Additional material included portions of the vertebrae (cases 2,3), proximal femur (cases 2,3,4), proximal humerus (case 4), and distal radius and ulna (case 5). In addition presumably normal skeletal components from stillborns and neonates (generally with cardiovascular abnormalities) were utilized for comparison.

Cases 1 and 2 showed pathologic changes that can be considered indicative of the acute stage of the disease. Case 5 (Figs. 15–17) represents a disease process of several weeks duration, but still should be classified as representative of acute pathologic change. Cases 3 and 4 (Figs. 18,19) showed the chronic consequences of the treated, acute disease. Thus, a reasonable survey of the spectrum of pathobiologic change was possible.

The earliest evidence of involvement was the accummulation of inflammatory cells and bacteria in the primary spongiosa of the metaphysis. This occurred among the trabecula, but without any significant damage to the trabecula. These multiple small foci then spread latitudinally so that much of the primary spongiosa was involved (Fig. 8B). Interestingly, the inflammatory process rarely extended beyond the primary spongiosa, implying that a cellular (reticulo-endothelial) defense mechanism may have been functional at this level of osseous maturation. In other regions, rather than spreading latitudinally the inflammation tended to localize and enlarge. As it

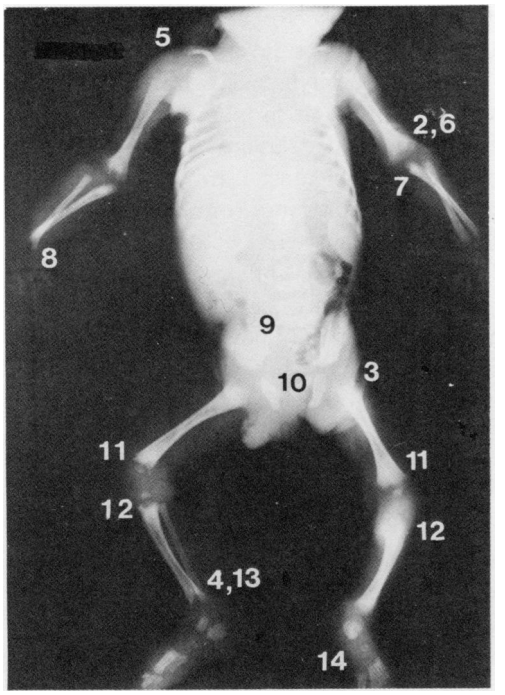



FIG. 1. Post-mortem roentgenogram showing osteolytic destruction of multiple metaphyseal regions of the upper and lower skeletal components. Most of these will be shown in greater detail grossly and histologically in subsequent figures. The numbers adjacent to involved regions refer to the detailed illustrative figures. The distal left femoral ossification center was shifted laterally, suggesting an epiphyseolysis. The distal right tibia exhibits a lytic lesion that proved to be a membrane-lined abscess (Brodie's abscess). On the basis of the roentgenographic appearances it was impossible to tell whether the lytic lesion represented cortical destruction (e.g., Fig. 2) or an intraosseous abscess with intact cortex (Fig. 4).

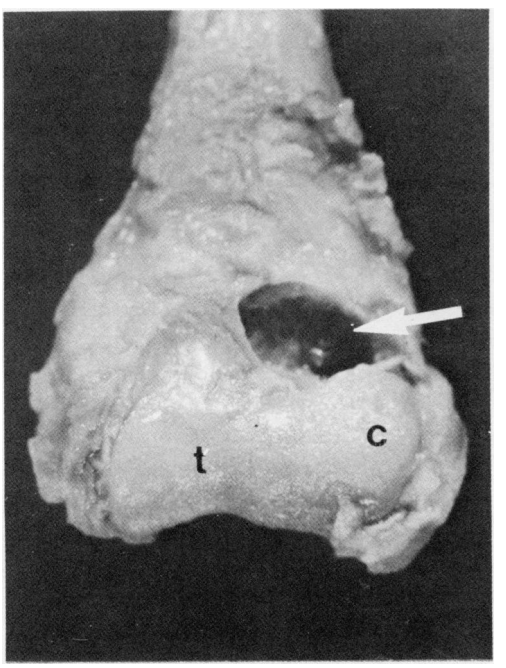



FIG. 2. Osteolytic anterior cortical defect of distal left humeral metaphysis above capitulum (c). The metaphysis over the trochlea (t) was intact. The metaphyseal osteomyelitic focus had decompressed into both the elbow joint and subperiosteal tissue because of the course of the capsular attachment. Histologic details are shown in Fig. 6.

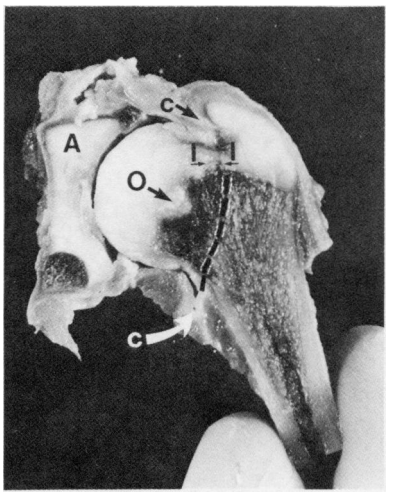



FIG. 3. Coronal section of left hip showing acetabular cartilage (A), proximal femoral chondroepiphysis, including the intraepiphyseal continuity (I) between capital femur and greater trochanter, and a focus of osteomyelitis (O) destroying epiphysis, physis, and metaphysis. In contrast the metaphysis under the trochanter and intraepiphyseal region appeared grossly intact. The dark line across the femoral neck defines the capsular (c) attachment and emphasizes the intracapsular location of the medial metaphysis, a major factor allowing decompression of the osteomyelitis into the hip joint. Histologic details are shown in Fig. 10.

enveloped the trabecula they become necrotic and essentially formed microsequestra. Osteolytic dissolution appeared to be a chemical process, as no osteoclastic destruction of bone was evident in these abscess foci. Similarly, when a significant inflammatory process spread latitudinally the newly formed trabecula were rendered ischemic and underwent highly variable osteolysis.

The metaphyseal abscess in a few instances formed a localized region with a fibrous wall (Figs. 7B,13B). This was variable in size, was sometimes surrounded by reactive bone, and sometimes by inflammatory tissue. This pattern of abscess formation represented a Brodie's abscess. In one instance the abscess decompressed spontaneously into the joint (Fig. 13B). Each abscess had a membranous fibrous lining.

Interestingly, when the right and left sides were compared for any given epiphysis,

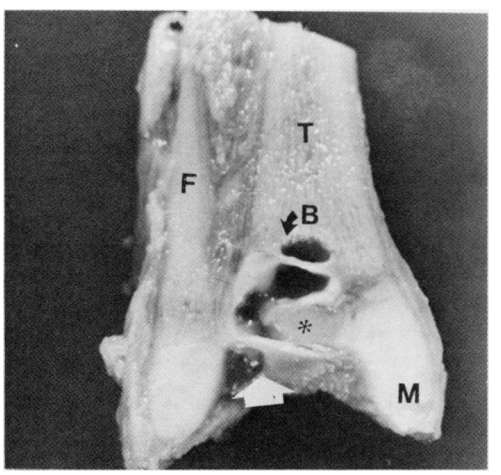



FIG. 4. Right distal tibia and fibula showing Brodie's abscess cavity (B) which decompressed through the syndesmosis into the ankle joint (*arrow*). Note the translucent appearance (*) of the hyaline epiphyseal cartilage contiguous with the abscess and physeal damage, as compared to the normal opaque white appearance in the medial malleolus (M) and fibula. Histologic details are shown in Fig. 13.

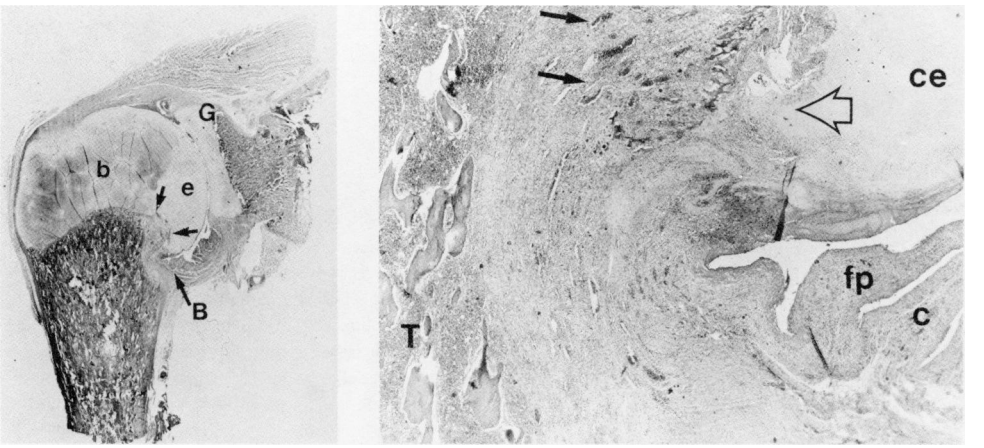



FIG. 5. A. Coronal section (2X) of right proximal humerus and glenoid (G). The primary focus of osteomyelitis is present in the medial metaphysis, but has also directly destroyed the medial physis and thereby invaded the epiphysis. There also was extension into the subperiosteal space and the joint on one side. The hyaline cartilage was being destroyed directly by the inflammatory process in those areas where the physis had been lysed. The process had also invaded the medial portion of the cartilage canal system and was extending further into the epiphysis, toward the secondary ossification center. Similar invasion of the glenoid metaphysis and epiphyseal vessels was evident. Where the growth plate was intact the epiphyseal hyaline cartilage was normally basophilic (b). However, where the physis was destroyed the cartilage took on an eosinophilic stain (e). This metachromasia correlated, respectively, with the opaque and translucent appearance of the cartilage in the gross specimens, no matter which epiphysis was involved (e.g., see Fig. 4). The letter "B" indicates the area of the accompanying higher power view. B. 10X magnification of medial region in Fig. 5A showing destruction of a significant amount of metaphyseal bone and a few remaining necrotic trabeculae (*closed arrows*). Relatively normal trabeculae (T) also are evident. The open arrow indicates the region where the growth plate has been completely destroyed. The fibropurulent material (fp) extends into the joint. ce—chondroepiphysis, c—capsule.

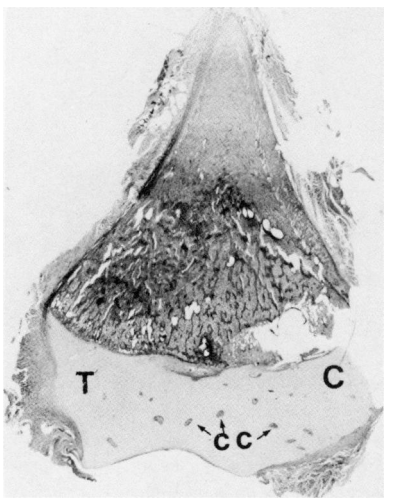



FIG. 6. Coronal section (2.5X) of distal humerus showing osteomyelitic focus over the capitulum (C), corresponding to the defect seen in Fig. 2. The physis had also been destroyed. In contrast the metaphysis and physis associated with the trochlea (T) were relatively undisturbed. There was minimal invasion of the cartilage canals (cc).

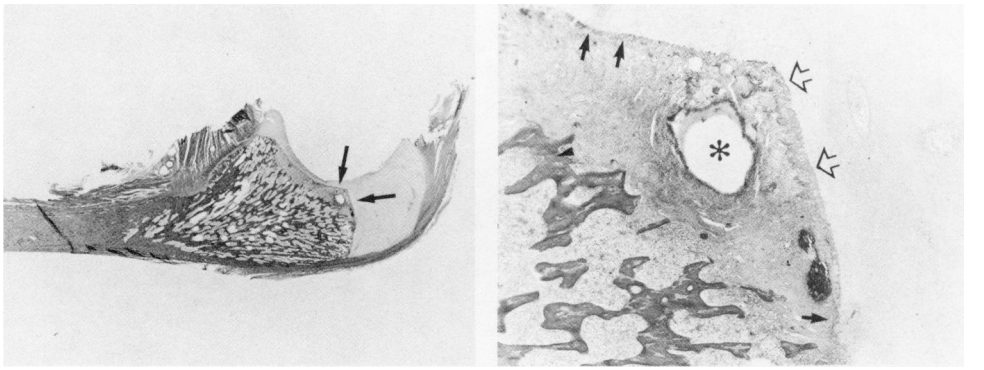


FIG. 7. A. Low power (2X) of proximal ulna and olecranon showing intact physis juxtaposed to a metaphyseal focus with trabecular destruction (*arrows*). B. Higher power (8X) showing early formation of a Brodie's abscess (*) in region of fibropurulent tissue that had destroyed significant amounts of primary spongiosa. In particular the subchondral metaphyseal bone was variably intact (*open arrows*) or damaged (*closed arrows*). However, the cartilage columns and germinal cells were intact.

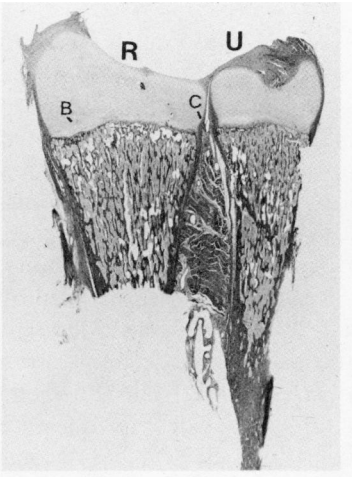
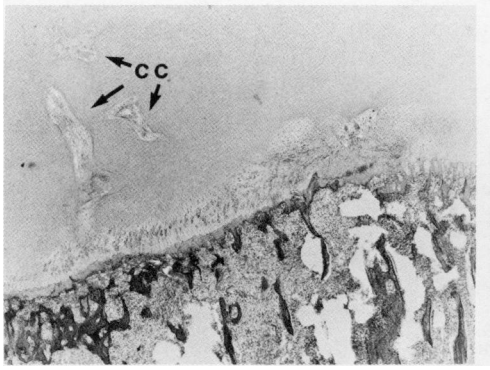
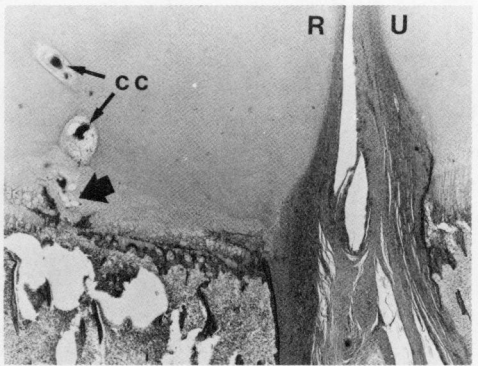



FIG. 8. A. Coronal section (2X) of distal radius (R) and ulna (U), showing mild involvement compared to other regions. B and C refer to the higher power photomicrographs. The ulna had diffuse metaphyseal inflammation, but the physis was intact and the cartilage canals free of disease. The radial physis was damaged in a few areas, although the bulk of the physis was intact. B. Higher power (10X) showing osteomyelitic process throughout the metaphyseal trabeculae, many of which are necrotic (*darker staining*), a relatively normal subchondral region and physis, and a normal cartilage canal system (cc). Toward the right side of the section an area of physeal invasion is evident. C. Magnification (10X) of peripheral region where osteomyelitis has crossed the physis (*large arrow*). The cartilage canal system (cc) shows thrombosis of the central artery and vein.



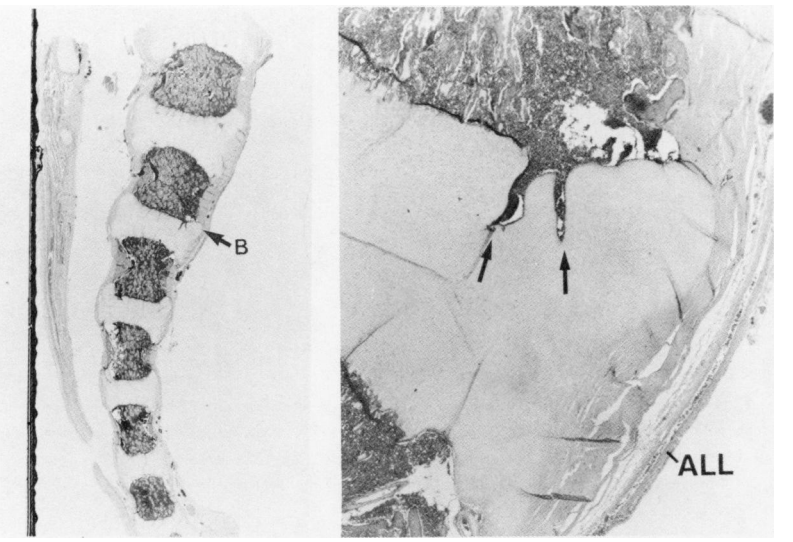



FIG. 9. A. Sagittal section (2X) of lumbosacral vertebra, showing minimal destruction of vertebral centra and intact chondroepiphyseal and disc space regions. B. Higher magnification (10X) showing inflammatory process, extending into two transphyseal canals (*arrows*). ALL—anterior longitudinal ligament. There was absolutely no evidence of disc space involvement.

the major focus of inflammation was always similarly located. This implies a certain selectivity of blood flow to certain regions, or a particular susceptibility to infection.

The major pathway of spread from the metaphyseal focus was latitudinally toward the normally fenestrated metaphyseal cortex (Fig. 20). The inflammation penetrated through the interstices of the cortical bone. In some instances osteolytic destruction of the cortex led to a large, pathologic opening. Once through the cortex the pus spread in one of two ways. Most commonly it reached the subperiosteal space, hydrostatically elevated the periosteum and spread around areas of the bone, effectively sequestrating larger areas of cortical bone. Reactive bone was formed by the elevated periosteum (Fig. 17). If capsular (synovial) attachments extended into the metaphysis, making a metaphyseal segment intra-articular, decompression occurred into the joint. In Case 1 this happened in only one shoulder, one elbow, one hip, and one ankle, even though similar foci of metaphyseal osteomyelitis were present bilaterally at each joint. At the hip the septic arthritis also further decompressed by breaking through the posterior capsule, surrounding the sciatic nerve in the process (which would explain the pseudoparalysis present in the leg).

Perhaps the most important finding, and one which was present to a variable extent in all five cases, was specific damage to the physis. This appeared to be due to two distinct mechanisms. First, and most common, was a progressive invasion of the various physeal layers. The inflammatory process filled the cell columns, destroying the transverse septa and replacing the chondrocytes. The next stage was destruction (probably enzymatic) of the longitudinal septa between the original cell columns. This allowed transverse spread. In some instances this was extensive, leading to complete or almost complete loss of the hypertrophic zone, while in other regions only a small number of cell columns were involved. Undoubtedly as long as only the hypertrophic region was involved, continued physeal growth was possible. However,

in a few cases the inflammatory process continued and involved the germinal layers as well. Again, this level of cellular damage was highly variable. The second mechanism appeared to be extension of the infection along transphyseal canals, with centrifugal expansion of the inflammation toward the surrounding cell columns.

When extensive transverse spread of the inflammation occurred, there was a purulent membrane between remaining epiphysis and metaphysis. This allowed some displacement (epiphyseolysis) of the contiguous skeletal components (Fig. 11B). In other cases (Fig. 16) the physis was rendered partially unstable from the partial destruction, and then fractured through the remainder of the physis in an undulating fashion.

Once the growth plate had been breached then the inflammatory process further invaded the epiphysis by two mechanisms. Direct destruction by chondrolysis of the matrix appeared to be most common. However, by spread through the transphyseal

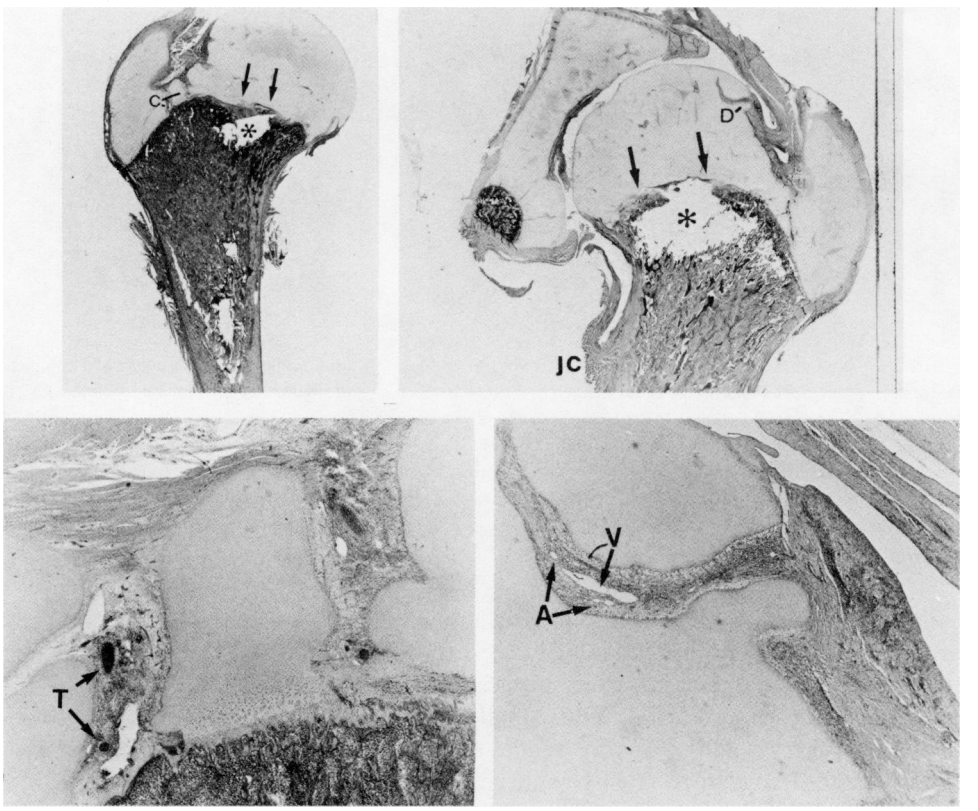



FIG. 10. A. and B. Coronal sections (2X) of right and left proximal femurs showing essentially identical foci of inflammation (*) in each side. This involvement of the mid-region of the capital femoral metaphysis allows decompression into the joint, which occurred only on the left side. Note the joint capsule (jc) attaches beyond the infection, predisposing to intraarticular rather than subperiosteal decompression. The physis overlying each focus of infection had been destroyed (*arrows*), although adjacent medial and lateral regions (especially under the greater trochanter) were intact. C and D in these figures refer to the accompanying higher power photomicrographs. C. Higher power (10X) showing intraepiphyseal branches of the medial circumflex artery, which normally communicate across the intraepiphyseal portion of the chondroepiphysis to supply regions of the metaphysis. The perivascular spaces are filled with inflammatory tissue and there are numerous intravascular thromboses (T). D. Higher power (10X) of fibropurulent filling the branches of the posterosuperior system as they enter the chondroepiphysis. The central artery and vein were not thrombosed.

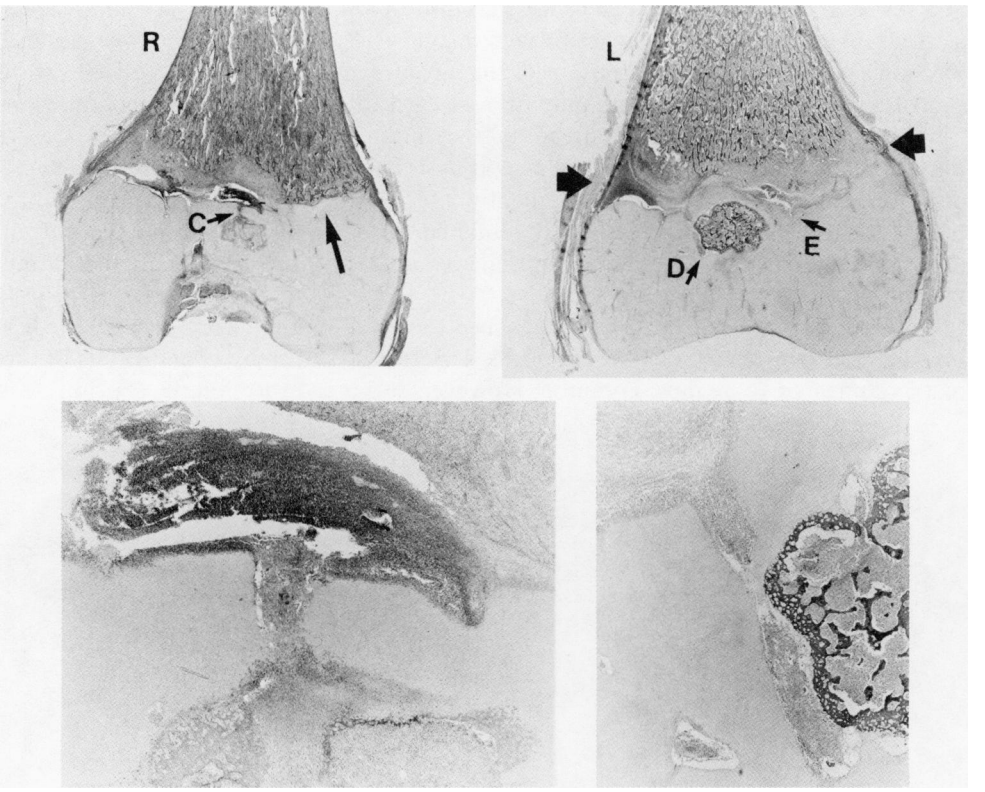



FIG. 11. A. and B. Coronal sections (2X) of right (A) and left (B) distal femurs. The left femur had complete destruction of the physis and juxtaphyseal metaphysis (*arrows*) which had allowed the epiphyseolysis evident in Fig. 1. On the right side the medial portion of the metaphysis and physis was intact (*arrow*), although both areas were destroyed laterally. The right secondary ossification center showed significant inflammatory destruction compared to the left. C and D. Higher power (10–12X) views of extension of osteomyelitis through transphyseal and cartilage canals. In C the process has extended directly from the metaphysis (*top*) through a canal system to reach the secondary ossification center (*bottom*). In D a similar process involves a canal system just peripheral to the secondary ossification center, which has more bone present than C.

canals as well as spread into the cartilage canals directly from the epiphyseal invasion, the purulent process gained access to the cartilage canal system. This led to thrombosis of vessels and external occlusion by volumetric expansion of the inflammation within the canal. The overall effect was to render sections of the growth plate ischemic, which probably made them more susceptible to inflammatory invasion and destruction. The ischemic changes also affected the secondary ossification center, allowing spread of the inflammation into this osseous area also (Fig. 11C).

In the "chronic" specimens major areas of destruction were evident. Significant portions of the cartilaginous epiphyses of the proximal humerus and proximal femur had been totally destroyed. The remaining cartilage had fibrous replacement in some areas, and particularly in the proximal humerus there was a fibrovascular bridge going across the physis. The growth plate was variably functional. Areas near fibrous bridging showed loss of cell columns and irregular clone formation. Longitudinal growth, as indicated by cell column height, was less than expected (compared to normal specimens available in the Skeletal Growth and Development Study Unit

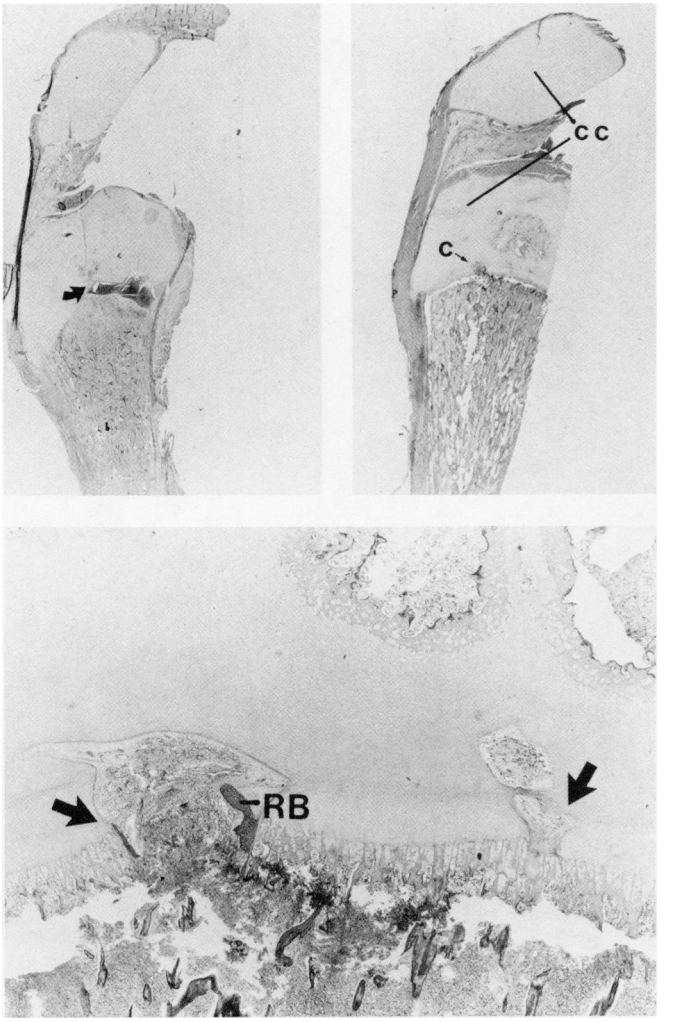



FIG. 12. A. Sagittal section (2X) of right proximal tibia showing a large focus of osteomyelitis causing epiphyseal and metaphyseal destruction. The chondrolytic process has almost reached the secondary ossification center (*arrow*). The tibial tuberosity is involved minimally. B. Sagittal section (2X) of left proximal tibia showing less severe involvement of the metaphysis and a relatively intact physis. The cartilage canals (cc) of the upper chondroepiphysis and patella were uninvolved. "c" indicates the region shown at higher power. C. Magnification (10X) of two areas of penetration of the physis through presumed cartilage canal systems (*arrows*). The larger area has some reactive bone (RB) at margins. The remainder of the growth plate is essentially normal.

collection). Of further significance was continuation of a low-grade inflammatory process within the primary spongiosa (no bacteria were seen with specialized stains). Variable areas of the physis were incapable of participation in active longitudinal growth, but did seem capable of random endochondral ossification. Other areas of dysfunctional physis had been "left behind" by longitudinal growth, and had formed clusters of cartilage within the metaphysis. Some of these were being replaced by bone, while others seemed to be incapable of osseous replacement (Figs. 18,19).

## DISCUSSION

Lannelogue, in 1879, first suggested a metaphyseal localization for osteomyelitis in children [10]. Lexer, in 1896, proposed that the nutrient artery was the primary route [10]. These ideas have become accepted concepts of basic pathogenesis, although contributions from other, smaller vascular systems, such as the metaphyseal arcade adjacent to the zone of Ranvier or the epiphyseal vessels, cannot be excluded [41,49]. Koch [55] demonstrated that intraosseous innoculation of bacteria localized in the metaphyseal veins within two hours. Hobo [56], working with skeletally immature

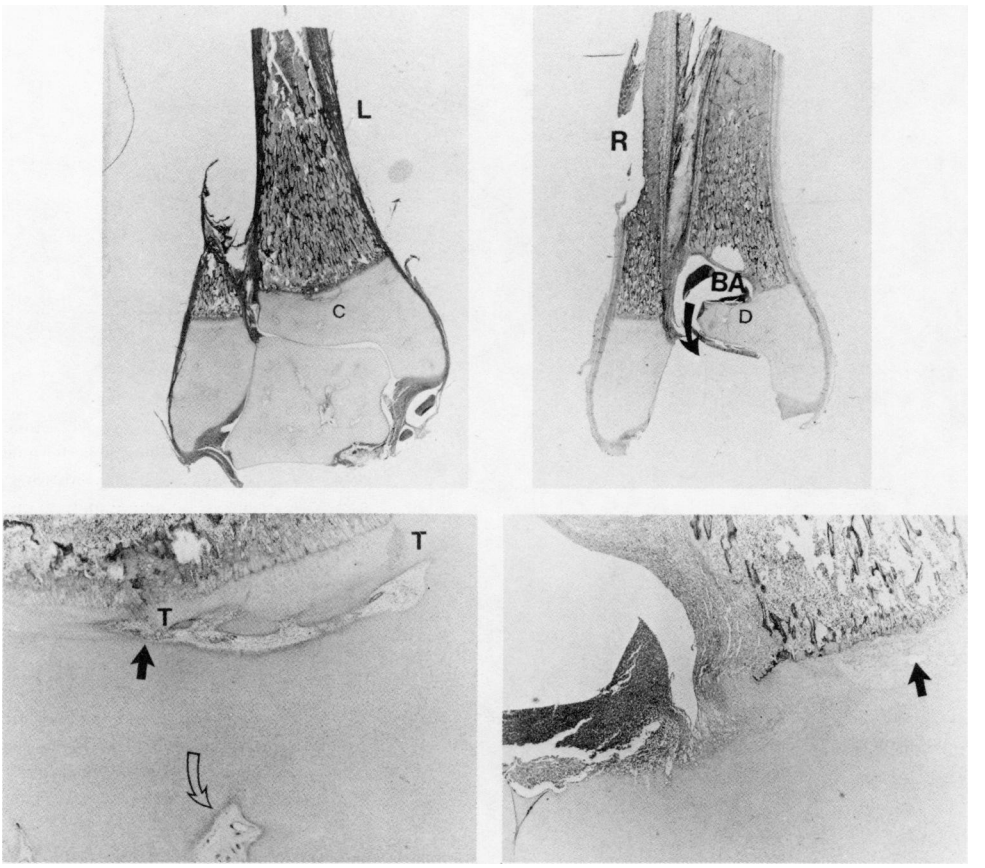



FIG. 13. A. Coronal section (2.5X) of left distal tibia (reversed for comparison with Fig. 13B) showing minimal metaphyseal and epiphyseal destruction. The cartilage canal systems have minimal inflammatory involvement. Most of the metaphyseal osteolysis is localized to the lateral side. The fibular growth plate was intact, although there was metaphyseal infection. B. Coronal section (2X) of right distal tibia showing Brodie's abscess (BA) with decompression along syndesmosis into the tibiotalar joint. The articular surface showed vacuolization and fragmentation of the cartilage. "C" and "D" in these views refer to the accompanying higher magnifications. C. Higher power (10X) of epiphyseal canal system and two transphyseal (T) areas. There is a localized focus of inflammation in one canal (*closed arrow*) because of retrograde extension of the process from the metaphysis through the transphyseal communications. An adjacent canal system (*open arrow*) did not exhibit similar perivascular involvement. D. Higher power (10X) of right tibia showing abscess destruction of the physis laterally and relatively intact physis medially (*arrow*).

rabbits, showed that the vascular arrangement—metaphyseal sinusoids—adjacent to the growth plate predisposed to localization of the infected bacteria. Starr [37] suggested the organisms responsible for bone infection were carried in the blood stream until they reached "the finer capillaries of the juxtaepiphyseal region of long bone," but he attributed establishment of the infection to lowering of an indeterminate "general resistance" of the patient rather than physiologic localization of the bacteria. Wilensky [57] described metaphyseal "fixation points" and supported the concepts of Hobo. Leveuf [25] refuted that osteomyelitis in the child initially localized in the metaphysis, and instead favored thrombosis of the main trunk of the nutrient artery, as originally proposed by Hart [6].

These various ideas were conjectural, based primarily upon clinical observation and a few experimental studies using animals with a much less developed epiphyseal/

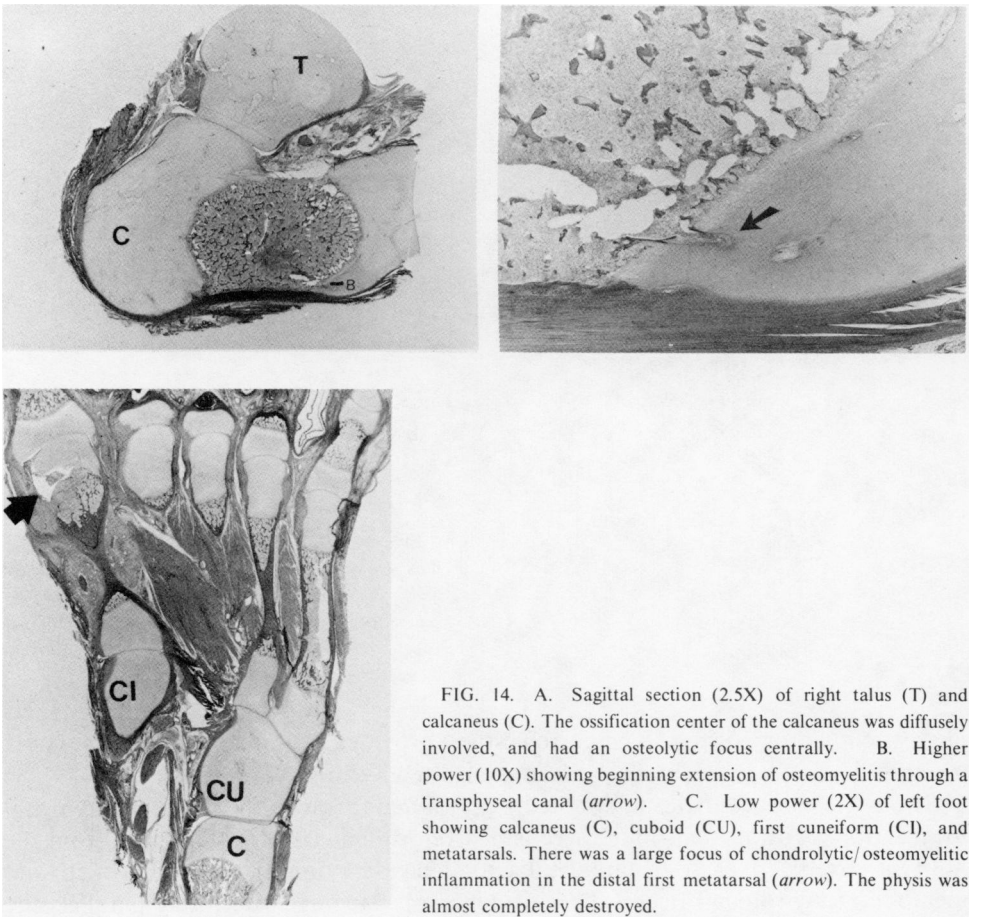



FIG. 14. A. Sagittal section (2.5X) of right talus (T) and calcaneus (C). The ossification center of the calcaneus was diffusely involved, and had an osteolytic focus centrally. B. Higher power (10X) showing beginning extension of osteomyelitis through a transphyseal canal (*arrow*). C. Low power (2X) of left foot showing calcaneus (C), cuboid (CU), first cuneiform (CI), and metatarsals. There was a large focus of chondrolytic/osteomyelitic inflammation in the distal first metatarsal (*arrow*). The physis was almost completely destroyed.

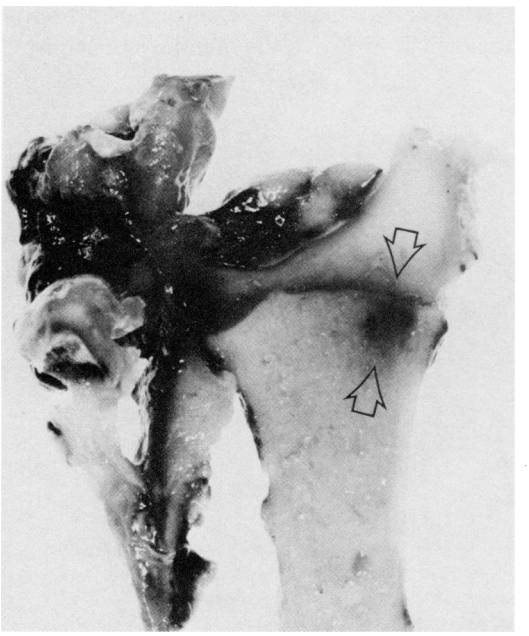


**FIG. 15. (Case 5). Coronal section of distal radius and ulna showing metaphyseal focus of osteomyelitis (*arrow*), with very little grossly evident destruction in remainder of the trabecular bone.**

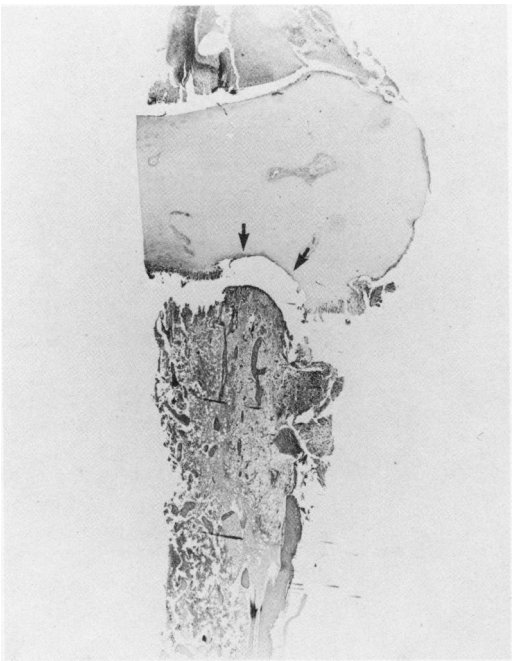


FIG. 16. (Case 5). Higher power (5X) of distal ulna showing epiphyseolysis. Notice that the physis and metaphysis are irregularly involved, with the separation extending into regions of the germinal zones. Variable areas of the physis were directly damaged by the infection (*arrows*).

physeal circulatory system. The current study provides definitive histologic support for an initial metaphyseal focus in neonatal osteomyelitis.

Rheologic characteristics undoubtedly play a major role in the initial metaphyseal localization. Within each bone there is a proportionate flow distribution from the nutrient artery to each metaphyseal end dependent upon rates of growth and metabolic (physiologic) needs. The incidence of osteomyelitis closely parallels the percentage growth contributions of each epiphysis/physis. Second, microcirculatory anatomy in the juxtaepiphyseal metaphysis appears to play a role, once the appropriate aliquot of bacteria is presented by the nutrient artery to the metaphysis. Robson

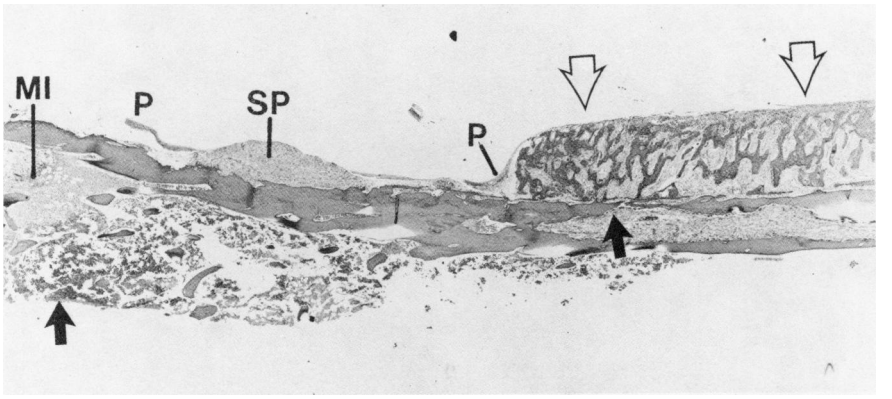



FIG. 17. (Case 5). Subperiosteal new bone formation (*open arrows*) along the distal ulnar diaphyseal cortex. There is a distinct difference between the antecedent (preinfection) mature cortical bone and the new membranous bone. In some regions active bone destruction was occurring (*closed arrows*). P—periosteum, SP—subperiosteal inflammatory process, MI—metaphyseal infection.

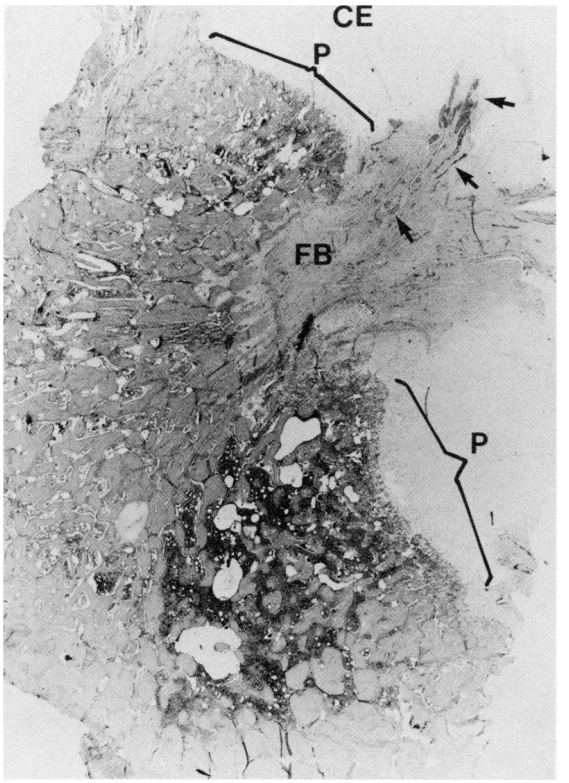



FIG. 18. (Case 4). Low power (12X) view of proximal humerus showing chronic changes secondary to chondrolytic destruction of most of humeral chondroepiphysis (CE). A fibrovascular bridge (FB) connects the metaphyseal (*left*) with the remaining epiphysis (*right*). The vascularity within the fibrous tissue is evident (*closed arrows*). This tissue had completely replaced the physis (P). On either side of the fibrovascular bridge the physis was irregular, forming small clones similar in appearance to osteochondromatous endochondral cartilage/bone transformation. Other areas of the physis further away were normal in appearance. The metaphysis was still filled with chronic inflammatory tissue (*darker areas in lower half of photomicrograph*).

[58] has shown that cutaneous and subcutaneous, clinically evident infections depend on a finite number of bacteria per unit volume ($10^5/cm^3$), and it is not unreasonable to assume similar quantitative factors are integral in the inception of a focus of osteomyelitis. Higher volumes of blood flow would carry a greater absolute number of bacteria to the potential focus. However, preliminary studies of an animal model suggest high epiphyseal and diaphyseal bacterial concentrations for two to three

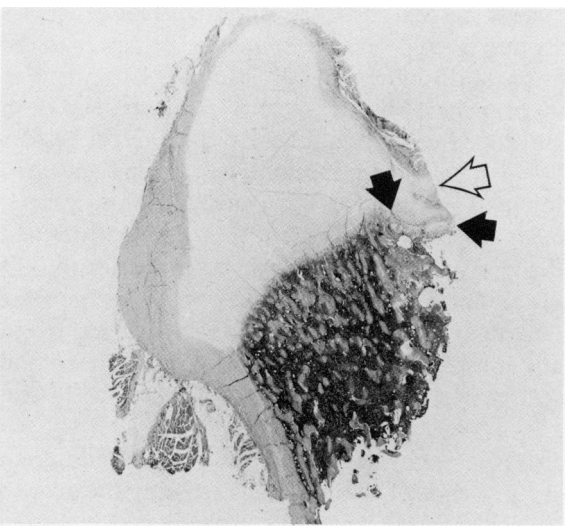


FIG. 19. (Case 4). Macroscopic appearance of proximal femur, showing similar destruction as in Fig. 18. This section essentially comprises the greater trochanter. A small area of intraepiphyseal cartilage remains (*open arrow*), while the capital femur (epiphysis, physis, and metaphysis) has been destroyed completely. The physis of the trochanter is relatively normal except in the region where the capital femur should have been. Here the physeal remnants are irregular and again forming clones rather than columns (*closed arrows*). As in Fig. 18, the darker staining regions among the trabecular bone represent chronic inflammation.

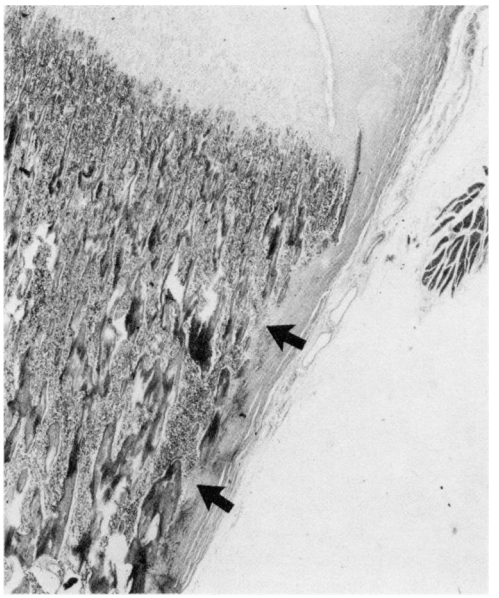


FIG. 20. Low power (15X) of normal metaphyseal/epiphyseal junction and metaphyseal cortex of a neonate (stillborn), showing presence of an incomplete (fenestrated) cortex and continuity of the intertrabecular soft tissue elements and the periosteum. These fenestra are a ready anatomic egress for the spread of metaphyseal osteomyelitis into the subperiosteal space (or joint, if this area happens to be intracapsular, as in the proximal femur). The infection may decompress easily through these spaces without necessarily causing a large defect.

hours, and an initially low metaphyseal concentration which increases dramatically within twelve to twenty-four hours, while the epiphyseal and diaphyseal counts drop to virtually zero [59].

Trueta [10] was the first to suggest that changing vascular arrangements during skeletal maturation, particularly in the microcirculation, might be responsible for the changing patterns of childhood osteomyelitis. The capillarity to the metaphysis has a double origin. The peripheral vessels adjacent to the zone of Ranvier are derived from a periosteal plexus, while the majority of the circulation are the terminal ramifications of the nutrient artery. After turning in acute loops at the zone of ossification, these vessels form larger sinusoidal veins. This is a region of relative rheologic stasis, and appears to be the first region where the bacteria localize [59]. This localization may cause thrombosis in the sinusoids. The arterial side of the metaphyseal loops is probably secondarily (retrogradely) thrombosed. This process is undoubtedly enhanced by the recently described process of rouleaux formation in the arterial loop [60]. Retrograde extension of thrombosis could lead to involvement of larger sections of the nutrient artery branches, but complete thrombosis, except in overwhelming sepsis similar to the current case, seems unlikely. Other factors besides the rheologic characteristics probably also enhance bacterial localization. This area has a poorly developed reticulo-endothelial system to assist in local infection control. Kahn [35] also suggested the trabecular structure predisposed to microfractures and clot formation, which would provide a growth medium. However, most cases in the neonatal period have no recognizable trauma. Kahn's hypothesis would seem more tenable in the older, active child. The relative weakness of the primary spongiosa centrally and fenestration peripherally must contribute to the transverse spread and eventual traversal of the metaphyseal cortex into either the joint or subperiosteal space.

The major factor that makes neonatal, as well as infantile, osteomyelitis different from older children appears to be the presence of blood vessels crossing the growth plate. Trueta [10] described such vessels, based primarily upon injected/cleared

specimens, but with no histological support. Ogden [47–49] has recently demonstrated these vessels in histological sections, and has defined them by the terms "transphyseal" or "communicating vessels." Trueta [10] described these vessels as "metaphyseal vessels penetrating the growth plate into the epiphysis, where they expand and form large venous lakes resembling metaphyseal venous sinusoids situated close to the epiphysis" (i.e., physis). However, the function appears to be one of venous drainage from the epiphysis. Further, no "lakes" were observed on the epiphyseal side [47–49]. The current histologic specimens showed retrograde extension of the infection from the metaphyseal sinusoids along these transphyseal vessels into the epiphysis.

The epiphyseal circulation varies considerably, depending upon whether the epiphysis is primarily cartilage or bone. Vessels enter in regions characteristic for each epiphysis, usually along points of capsular and perichondral attachments. These changing patterns of epiphyseal vascularity, especially during infancy, undoubtedly play a role in spread of infection, degree of damage, and potential for recovery. Blood vessels enter, traverse, and leave the epiphysis within structures termed cartilage canals. These canals course throughout the chondroepiphysis, supplying discrete regions, with minimum anastomosis between cartilage canal systems. These canal systems also supply, initially on an end-arterial, segmental distribution basis, the resting/germinal zones of the physis. In the late fetal stages and for varying lengths of time in postnatal development, the venous circulation communicates across the growth plate, anastomosing with the metaphyseal circulation. These vessels traversing the growth plate (transphyseal sinusoids) tend to be more common in the large epiphyses (proximal femur, distal femur, proximal tibia, proximal humerus) for several months, but become less frequent as the secondary ossification center forms and enlarges [43–49]. By the time the secondary ossification center forms a discrete subchondral bone plate over the physis, no vessels cross the growth plate. The relevance of these observations to the changing patterns of osteomyelitis in the various stages of pediatric osteomyelitis thus is more clear. First, there is a good correlation of more severe damage to the growth plate and chondroepiphysis in the epiphyses that normally have greater numbers of transphyseal vessels. Second, because the vessels that supply the epiphyseal growth plate are often derived from different canal systems than the remainder of the epiphysis, invasion of the transphyseal vessels does not necessarily mean initial spread throughout the chondroepiphysis. This again was quite evident in epiphyses such as the distal radius and ulna, distal fibula and proximal ulna, where an occasional involved transphyseal vessel was found, but the major cartilage canal system was uninvolved. In the distal humerus there was moderate damage to the growth plate associated with the capitulum, but not that associated with the trochlea; the major proportion of the cartilage canal system over both regions was free of disease. Further, in the carpal and tarsal bones, only those with an ossification center (e.g., calcaneus) had evidence of infection, but always in the bone and rarely in the cartilage.

Once the ossification center forms and begins to enlarge, the pattern of circulation of the epiphyseal vessels changes. Several previously end-arterial cartilage canal systems send vessels into the ossification center, thereby creating anastomoses between canal systems. Thus, the ossification center becomes a focus for more diffuse spread of infection within the chondro-osseous epiphysis. Again, this was quite evident in the larger epiphyses with ossification center formation (distal femur, proximal tibia). These regions had infection within the secondary ossification center and spread of infection throughout the cartilage canal system.

In the neonatal period particularly, and less so as the child grows, the metaphyseal cortex near the physeal periphery is fenestrated (Fig. 20), rather than being made up of dense lamellar bone. There is continuity of marrow soft tissue components with the subperiosteal tissue through these fenestrations. When osteomyelitis is present it may easily "decompress" into the subperiosteal space through these fenestrations, without ever having to create a large osseous defect. Because of this a large inflammation may continue within the metaphysis, while a second process enlarges in the subperiosteal region, not unlike a collar button abscess in the hand. This is one of the major reasons why a surgical opening must be made in the cortex to decompress the abscess or inflammation completely.

The hematology of neonates seems to render them more susceptible to infection. This may be related to hypofunction of the antibody, complement, phagocyte pathway, which is a temporary situation in the newborn. Kuo et al. suggested immunodeficiency beyond that normally encountered in the neonate could have been responsible for about half the cases of neonatal osteomyelitis and septic arthritis in their series [61]. Boxer et al. found granulocyte dysfunction in an infant unable to produce pus [62]. The neutrophils possessed a poorly polymerizable actin and exhibited abnormal locomotion, ingestion, and degranulation. Wright et al. showed decreased bactericidal activity of leukocytes of stressed neonates [63]. The abnormality was most evident against *S. aureus* and was principally a killing defect, while against *E. coli* both phagocytosis and killing were abnormal. Zipursky et al. found the neutrophil count to be unreliable as an indicator of sepsis and that thrombocytopenia was a more frequent concomitant of sepsis in neonates [64].

The growth plate classically is described as a barrier resistant to infection. However, as seen by this author and as described by others [23,35], osteomyelitis in older children may cross the growth plate and even extend into the joint. This is probably due to focal, direct bacterial/enzymatic destruction of a small area of the growth plate. The fact that major growth abnormalities do not ensue probably relates to the remaining growth potential and the non-peripheral location of the penetrating abscess.

Trueta [10] suggested that the physis was damaged much more frequently in infancy than later childhood. However, he was unable to corroborate this conjecture with any pathologic specimens. These studies conclusively prove his hypothesis of direct growth plate damage, and further support his contention (again hitherto histologically unproven) that the route is transphyseal spread and subsequent epiphyseal (i.e., "E" vessel) ischemia.

Several authors have described growth plate damage [5,19–29]. If only the metaphysis were affected, as would be assumed if the phenomenon of lack of physeal damage were accepted, it becomes difficult to explain those subsequent growth deformities, which, by serial X-rays, affect the epiphysis as well as metaphysis. Further, other authors have described growth deformity followed by "spontaneous correction" [30–33]. What is the mechanism of these latter observations? Silverman [65], in describing a recovery of "epiphyseal invagination" in a case of scurvy, implied resumption of metaphyseal and epiphyseal ossification, as well as accelerated cartilage and bone growth in the area of the defect. Observations of the highly variable involvement in these cases suggest the following mechanism. The initial damage leads to replacement of segments of the physis, epiphysis, and metaphysis by fibrous tissue, which will not necessarily cause epiphyseodesis. The cartilage canal system is, for the most part, unaffected. The hyaline cartilage is undifferentiated and would eventually become part of the secondary ossification center. It is not untenable

to suggest it may help regenerate portions of the damaged physis, especially if small. Finally, diametric expansion of the still intact physis could slowly fill in the defect. Thus, by gradual replacement and differentiation, the defect could be filled in, so that it would seemingly regenerate.

Trueta felt that extension of the infection into the epiphysis led to growth deformity because of epiphyseal vessel ischemia. This study supports the concept. Many of the "E" vessels were thrombosed by masses of inflammatory cells. However, this localized ischemic damage may not be irreparable. It is plausible that the undifferentiated hyaline cartilage of the adjacent regions of the epiphysis, an area that normally will further differentiate and undergo osseous transformation as part of the spherical growth plate of the secondary ossification center [48], could reform a discoid growth plate associated with the metaphysis. Further, the undamaged regions of the discoid growth plate might expand into the damaged area by diametric expansion. This clearly depends upon the degree and location of damage, and the state of epiphyseal maturation. The more severe involvement of the epiphyseal circulation seen in some of the epiphyses of the current case would seemingly make recovery improbable. New peripheral diametric expansion certainly may occur, but might lead to the development of unusual physeal contours.

Slipping of an epiphysis as a complication of metaphyseal osteomyelitis appears rare [34,66,67]. Undoubtedly the use of antibiotics in the early phases of the disease prevents the amount of destruction necessary to produce mechanical loosening. Siffert [34] felt a combination of factors was necessary for epiphyseal slipping: bone destruction in the metaphysis, local cortical perforation, and periosteal stripping and elevation. Well over fifty foci of osteomyelitis were found in the tubular bones of the current cases, but only two sites (cases 1 and 5) progressed to an epiphyseal slip. Examination of these two specimens showed all the aforementioned criteria. However, additional important changes were noted. First, bone destruction was not localized to a focus in the metaphysis and cortical edge, but rather involved the entire juxtaepiphyseal metaphysis and circumferential cortex, with replacement of the primary spongiosa by inflammatory cells and cellular detritus. Second, virtually the entire growth plate (all zones, including resting and germinal) had undergone chondrolytic destruction. Siffert felt the complication of epiphyseal slip, while rare, would result in complete remodeling (based on the accepted concept that physeal destruction does not occur). However, it is difficult to believe such regeneration would have occurred in these patients in view of the amount of physeal destruction.

Smith's classic review of septic arthritis of infancy, published in 1874, included thirteen fatal cases of several joints besides the hip joint [54]. He concluded that the septic arthritis usually resulted from a rupture into the joint of a metaphyseal, or occasionally epiphyseal, abscess. Since then several authors have concurred that septic hip disease is frequently preceded by a focus of osteomyelitis in the metaphysis [22,24,26,51,53]. The multiple foci of osteomyelitis in the first patient primarily decompressed into the subperiosteal and subcutaneous tissues. But in one shoulder, one elbow, one hip, one ankle, and one thumb (metacarpophalangeal) joint the metaphyseal infection had destroyed a portion of the intra-articular metaphyseal cortex and decompressed into the joint. Similar findings were present in cases 3 and 4.

The growth damage that accompanies septic arthritis, especially of the hip, has been hypothesized to be due to direct destruction of the epiphysis. However, Kemp and Lloyd-Roberts [14] recently suggested vascular ischemia due to inflammatory occlusion of the major blood supply. On the basis of the current observations, there

certainly is a degree of direct destruction of the articular cartilage, but also two additional mechanisms that further the degree of eventual damage. First, the growth plate may be significantly, but focally damaged, thus allowing variable regions of growth or lack of growth longitudinally. Second, the major arterial pathways supplying the epiphysis may be occluded. This latter observation supports the hypothesis of Kemp and Lloyd-Roberts.

One could argue that the joint infection is primary and then secondarily seeds and invades the epiphysis and metaphysis. However, the statistical evidence from these cases would not support such a concept. Well over fifty foci of metaphyseal osteomyelitis were observed in the tubular bones (major bones as well as smaller bones such as metatarsals, metacarpals, and phalanges), but only a few joints had septic arthritis. In each case the contralateral joint was uninvolved, *BUT* the same site of metaphyseal infection concentration was evident on each side. In no case was there a septic arthritis without contiguous osteomyelitis.

The mechanism of articular cartilage destruction has been discussed by Curtiss [68–70]. Of particular importance in joint infection is the appearance of enzymes. However, the presence and activity of these enzymes appears to show a positive correlation with the intra-articular white blood level concentration. These enzymes are contained particularly within the polymorphonuclear leukocytes. The synovial cells also contain lysosomal granules and acid phosphatase. Fibrin deposition, initiated by abnormal clotting mechanisms (not usually present intra-articularly), may also be a major factor in the mechanism of joint damage, inasmuch as the adherence of these deposits to the articular cartilage could (a) impair the entrance of nutritional material into the cartilage from the synovial fluid, a factor further complicated by the pain-induced joint immobilization and decreased synovial fluid dynamics, and (b) could also impede release of toxic metabolites from the articular cartilage. This adherence of fibrin was quite evident in the joints that had septic involvement in the first case. Fibrin also chemotactically may attract leukocytes, since these cells phagocytize fibrin as well as other particular matter. Degranulation of leukocytes and release of enzymes into the synovial fluid may then perpetuate and worsen the initial damage. Interestingly, while this phenomenon may be the mechanism in joint cartilage damage, it also seemed to be a possible mechanism for growth plate and epiphyseal cartilage destruction, since the margin between infection and normal hyaline cartilage was associated with a high concentration of polymorphonuclear leukocytes. The joint fluid in rheumatoid arthritis has a collagenase and abnormal prostaglandins capable of attacking articular cartilage. Such enzymes have not yet been described in septic arthritis, but there is a strong possibility they are present. It is also probable that an enzyme or enzymes are released which directly attack the intercellular matrix. These enzymatic processes would explain both the differential staining characteristics of the invaded hyaline cartilage and the vacuolization and fragmentation of the articular cartilage.

The first case had sciatic and femoral nerve palsy in the right leg. Such nerve injury has been described infrequently as a result of septic hip [17] or due to injection of the umbilical cord [18]. White [17] injected the normal hip of stillborns, and showed how dye filled the iliopectineal bursa anteriorly and distended the capsule posteriorly. In both instances in the newborn the nerves lie directly over these structures. Case 1 presented pathological correlation of the proposed hypothesis of the nerve injuries. In both instances the capsule had been disrupted and the purulent material had surrounded the nerve.

The variable role of causative microorganisms in chondrolytic and osteolytic

destruction is incompletely known. In all five cases in this study Staphylococcus proved to be extremely damaging. Fox and Sprunt [42], despite downplaying the need for surgical decompression, showed a fifty percent residual damage rate in the "Staphylococcal interval," but only a twenty-nine percent rate in the "streptococcal interval." Unfortunately, they had a high incidence of craniofacial osteomyelitis, and did not provide a breakdown of microorganism incidence versus area of involvement. Presumably the mandibular and cranial osteomyelitis would be expected to have a higher incidence of non-staphylococcal etiology. However, Fox and Sprunt [42] did report longitudinal growth abnormalities in neonates infected with group B streptococci and *E. Coli*. Certainly in older children non-staphylococcal microorganisms may cause significant skeletal destruction and growth damage, and may even mimic malignant osseous changes [71,72]. Therefore, while the histopathologic changes in the currently reported cases were all due to *Staphylococcus aureus*, it seems reasonable to assume that similar changes might occur with other microorganisms, especially since the initial focus appears to be metaphyseal. The variables may be the degree of metaphyseal damage, and the likelihood of physeal and epiphyseal invasion.

## CONCLUSIONS

1. These cases allowed detailed and gross histological demonstrations of the pathophysiology of osteomyelitis and septic arthritis in the neonatal period, and support the hypothetical and clinical concepts of the disease in the pediatric patient, especially during the first year of life.
2. The inception of the infection is metaphyseal, with certain areas in each bone being characteristically involved initially, and to a greater extent, prior to extension of the infection into the remainder of the metaphysis.
3. The infectious focus in the metaphysis usually spreads latitudinally by osteolytic destruction of the primary spongiosa and penetration of metaphyseal cortical fenestrations, as well as osteolysis of regions of the cortex. The abscess then drains into (a) the subperiosteal space, (b) the adjacent soft tissues by destroying the periosteum, or (c) the joint.
4. Joint involvement, by virtue of differences in the developing anatomy (i.e., capsular reflections) may be multiple, and not just the hip. In no joint was there a primary involvement—but rather an extension of the infection from the metaphysis. However, this may only be true for Staphylococcal infections. In contrast *Hemophilus influenza* appears to seed the joint primarily, rather than bone.
5. The growth plates (physes), which are well formed at birth, are *NOT* resistant barriers, as classically taught.
6. In infancy the growth plate is traversed irregularly by sinusoidal vessels (transphyseal vessels) that are derived from the epiphyseal circulation, appear venous in nature, and empty into the metaphyseal sinusoidal loops. Blood flow appears to be from epiphysis to metaphysis under normal physiologic conditions.
7. Osteomyelitis may spread retrogradely from the metaphyseal sinusoids along these transphyseal vessels into epiphyseal vascular system (contained within cartilage canals). Involvement of the particular epiphyseal vessels associated with the germinal layer of the growth plate may cause (epi)physeal ischemia.
8. The transphyseal vessels have a variable time of disappearance that appears to be directly related to the appearance and growth of the secondary ossification center. Once these vessels are no longer present, the growth plate becomes a reasonably effective barrier to spread of infection from the metaphysis. However, it is becoming

increasingly evident that the growth plate may be damaged in older children. This may be by direct destruction, rather than spread along a vessel, as occurs in the younger child.

9. Infantile osteomyelitis may cause direct destruction of variable areas of the growth plate by chondrolysis. However, the possibility that such sections of the physis were initially rendered ischemic by transphyseal/epiphyseal vascular invasion, and thus more susceptible to chondrolysis, must be considered.

10. After the growth plate has been destroyed, the infection may slowly advance into the hyaline cartilage of the chondroepiphysis. The gross appearance and the differential staining characteristics implied biochemical changes in the intercellular matrix (however, no attempt was made to ascertain qualitative chemical changes—this was an empiric observation).

11. The cartilage canal system allows a pathway for retrograde extension of the infection throughout the chondroepiphysis and into the secondary ossification center, where trabecular destruction similar to that in the metaphysis may occur.

12. The cartilage canal system may be occluded by spread of the infection in the perivascular space surrounding the central artery and vein, or by thrombosis. These lead to ischemia (avascular necrosis) of the hyaline and physeal cartilage of the epiphysis and the secondary ossification center.

13. In neonatal osteomyelitis the amount of growth disturbance is directly related to (a) the total area of the physis destroyed (relative to the total area of the plate), (b) the anatomical location of the destroyed area of the physis (i.e., central vs. peripheral), (c) the degree of concomitant destruction of the hyaline cartilage of the chondroepiphysis, and (d) the degree of damage to the cartilage canal/vascular system of the chondroepiphysis.

14. The septic joints showed vacuolization of the articular cartilage layers, with fragments breaking off into the joint, exposing underlying, undifferentiated hyaline cartilage of the chondroepiphysis.

15. Growth abnormalities in septic arthritides of infancy probably relate to destruction of the growth plate and portions of the epiphysis by the osteomyelitis process, as well as direct destruction from the joint sepsis, with both processes being integral to the overall destruction.

16. The nerve involvement in septic hip may be due to capsular distension and inflammation against the nerve, or penetration of the joint capsule to surround the nerve by purulent material.

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