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GENERALIZED HYPERTROPHIC OSTEOARTHROPATHY
A PATHOLOGIC STUDY OF SEVEN CASES *

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The association of digital clubbing with intrathoracic disease has been recognized since antiquity.[1] The wider distribution of the lesions of this malady with involvement of the shafts of the larger bones of the extremities has been appreciated only comparatively recently.[2,3] The syndrome which is termed generalized hypertrophic osteoarthropathy § may be defined as that condition occurring as a sequel of some major visceral disorder, usually intrathoracic in location, which is manifested by clubbing of the digits and ossifying periostitis, mainly of long bones, and is frequently associated with joint symptoms. Literature on the subject is not extensive and is for the most part concerned with the clinical findings, although the roentgenologic and gross pathologic features have been adequately described. During recent years Locke [4,5] and Mendlowitz [6] have recorded in detail the clinical aspects of the condition and Crump [7] has given an excellent analysis of the pathologic changes.

We have had the opportunity of examining the skeletal tissues from 7 cases of secondary hypertrophic osteoarthropathy in which all of the well known clinical and roentgenologic manifestations were represented. It is our purpose to present in detail the observed morphologic alterations in the bones and joints and to trace the sequences in the development of the major lesions of the syndrome.

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§ This nomenclature is preferred to the more frequently used term "pulmonary hypertrophic osteoarthropathy" in view of the occurrence of the condition in cases without evidence of pulmonary disease.

Material

The specimens serving as the basis for this study were obtained for biopsy or at necropsy from 7 men ranging in age from 18 to 65 years. Six of the patients had severe pulmonary disease and one suffered from congenital heart disease. Certain clinical pathologic data necessary for evaluation of the descriptive portions of the paper are presented briefly in Table I.

In order to facilitate presentation the observed changes have been described under four anatomical headings: *Periosteum, Cortex, Joints,* and *Clubbed Digits.* The description under each category is given as a composite of all the cases studied and is intended to portray, within the limits of the material available, the successive stages in the development of the peripheral lesions of generalized hypertrophic osteoarthropathy.

Pathologic Findings

Periosteum

In the early developmental stage of the osseous lesion the fibrous periosteum becomes thickened and exhibits signs of inflammation. Diffusely scattered lymphocytes in large numbers, less numerous plasma cells and, in some instances, polymorphonuclear leukocytes appear. Frequently the lymphocytes collect in dense aggregates in perivascular areas (Figs. 6 and 8). The adjacent extraperiosteal connective tissues are similarly affected but to a less marked degree. Coincidental with the appearance of the inflammatory reaction the periosteum becomes thickened and divided into two fairly distinct layers. The outer of these zones is more densely fibrous and it is here that the inflammatory cells accumulate in greater numbers. The inner cambial layer is comprised of one or several rows of swollen stellate or ovoid cells with vesicular nuclei and abundant amphophilic cytoplasm. Initially the fibrillary intercellular substance of this layer is loosely textured and edematous. This fibrillar material is soon replaced or obscured by the deposition of osteoid matrix. With this increment of new bone matrix, interposed between the original bone and the cambium (Fig. 5), the dual layered periosteum is displaced from the compact bone of the cortex.

Osteoid apparently is deposited first upon the dorsal or extensor surfaces of the affected bones and these predilective sites tend to exhibit a greater quantitative change throughout the disease. In the early phases the new bone exhibits no regular structure. Subsequently, however, as growth proceeds, the osteoid matrix assumes a palisade-like structure with poorly defined, homogeneous columns arranged perpen-

TABLE I

Clinical and Roentgenologic Data and Anatomical Sites of Material Studied

Case no.	Age	Underlying disease	Initial symptoms	Duration of underlying disease	Digital clubbing	Joint signs and symptoms			Bone tenderness	Roentgenologic examination		Material studied		
						Pain	Stiffness	Ankylosis		Clubbing	Long bones	Source	Bones studied	Joints studied
1	45	Pulmonary cancer	Pulmonary	3 yrs.	+	+	−	−	+	+	Marked periosteal lesion	Necropsy	Digits, tibia, fibula	Interphalangeal, ankle
2	38	Pulmonary cancer	Skeletal	2 yrs.	+	+	+	−	−	No films	Marked periosteal lesion	Necropsy	Tibia, femur	Knee
3	65	Pulmonary emphysema	Pulmonary	9+ yrs.	+	−	−	−	−	No films	No films	Necropsy	Digits	Interphalangeal
4	45	Pulmonary tumor	Skeletal	10 mos.	+	+	+	−	−	+	Marked periosteal lesion	Biopsy	Femur	Knee
5	52	Pulmonary cancer	Skeletal	Unknown	+	+	−	−	+	+	Marked periosteal lesion	Biopsy and necropsy	Digits, femur, tibia, fibula, patella	Interphalangeal, knee, ankle
6	18	Congenital heart disease	Cardiac	18 yrs.	+	+	+	−	−	+	No films	Necropsy	Digits	Interphalangeal
7	45	Pulmonary cancer	Skeletal	1½ yrs.	+	+	+	−	+	+	Marked periosteal lesion	Necropsy	Digits, metatarsals	Interphalangeal

dicularly to the bone surface (Figs. 7 and 8). With continued growth activity the periosteum displaces itself centrifugally, the columns are further elongated, and their deeper extremities become attenuated. They are then separated from each other by strands of edematous fibrous tissue not unlike that present in the cambial layer and probably representing prolongations of it (Fig. 8). This newly formed marrow tissue is highly vascular and contains a slight to moderate infiltration with lymphocytes. The trabecular narrowing is associated with active osteoclasis. In many regions, however, rows of osteoblasts remain and continue to add new layers of osteoid upon recently formed trabeculae (Figs. 6 and 8).

Shortly following its deposition the new subperiosteal bone layer becomes fused with the original cortical surface. Prominent cement lines persist, marking such points of union. The trabecular structure of the new bone also aids in distinguishing it from the pre-existing cortical compacta to which it is joined.

During periods of diminished periosteal activity mineralization progresses throughout the mass of osteoid and the palisaded columnar appearance is diminished or lost (Fig. 9). The peripherally situated new bone becomes more nearly continuous and, as a result of the union of many of the bony columns in this region, a pseudo-cortex is formed. This layer of condensed bone maintains its attachments to the true cortex by the persisting, radially arranged trabeculae. During such periods of relative inactivity the prominence of the cambial layer diminishes, the lymphocytic infiltration dwindles, and the periosteum returns to its resting stage (Fig. 11). The lesion may remain stationary at this stage or reactivation may occur.

Fluctuations in periosteal function probably are not wholly dependent upon activity of the basic disease in the thorax [6] but may be controlled in part by local factors since various phases of the skeletal lesions may be observed simultaneously in different bones in the same patient. There is considerable evidence of exacerbations and remissions in activity as attested by the appearance of the dual layered periosteum and the deposition of new columns of osteoid external to, but fused with, the thin pseudo-cortex described previously (Figs. 7 and 10). In this manner extracortical lamination is produced. As many as six such laminae have been described [8] although none of our cases exhibited more than two (Fig. 10).

As the result of centrifugal displacement of the periosteum the initially formed bone comes to lie at some distance from the cambium. In occasional specimens this distance was in excess of the thickness of the original cortex (4 to 6 mm.). Presumably as the result of physical stress

and variation in the vascular supply, and through the medium of osteoclastic activity, the original radial structure of the new bone is obliterated. The spongy textured bone replacing it soon acquires an arrangement similar to that of the normal cancellous bone of the medulla. The general alignment of the trabeculae is then parallel to that of the bony axis of the shaft (Figs. 11 and 12). The trabeculae gradually develop a normal internal lamellar structure.

The intervening marrow loses its fibrillar structure, becomes fatty, and occasionally evidence of focal hemopoietic activity is observed. Usually, however, there is no evidence of blood cell formation in the true medullary cavity at the same level. It is noteworthy that in the present study no constant abnormalities were found in the original marrow substance.

Coursing through the newly formed extracortical marrow are obliquely directed strands of fibrous tissue representing prolongations of fibers from the displaced periosteum. These penetrate to, and often into, the original cortical bone in the manner of Sharpey's fibers. They frequently encompass branches from the nutrient vessels in the original periosteum (Figs. 7 and 8). The subperiosteal bony trabeculae do not impinge upon or distort these fibrous strands. On the contrary it appears that the bone matrix is so deposited that it forms encasing tubular channels resembling Volkmann's canals.

At points of tendon insertion into the cortex an interesting variation of the periosteal disorder is encountered. Beginning at the tendo-osseous juncture and progressing into the tendons for distances up to 5.0 mm., there is progressive metamorphosis of tendinous tissue into fibrocartilage. The neighboring subperiosteal osteogenic lesion encroaches upon such areas and a replacement process simulating endochondral ossification may ensue (Fig. 13). The substitution of osteoid for fibrocartilage or hyaline cartilage is irregular and results in circumscribed but almost structureless masses of bone matrix. Ultimately, calcification occurs and the lesion assumes the appearance of an intratendinous osteophyte. A closely related change may appear in those ridges of bone to which membranous attachments occur (Fig. 14). This is particularly prominent in the linea aspera of the femur and the interosseous crests of the tibia and fibula.

The frequency and degree with which the various features of the periosteal lesion appeared in the present cases are shown in Table II.

Cortex

Following the deposition of subperiosteal bone and its fusion with the cortex as described in the preceding section, the configuration and

internal structure of the original diaphysis become modified. It has been indicated that the distinction between cortex and newly formed bone may be made during the greater part of the course of the disease. There is generally a slight difference in staining quality of the two parts and single or multiple cement lines persist at the points of fusion (Fig. 7). In long-standing lesions, however, these distinguishing features may become obscured (Figs. 10 and 11). In such instances it may be impossible to establish with certainty the limits of the original cortex. This is particularly true when, as the result of late changes, the structure of the latter has been modified (Fig. 12).

TABLE II

Summation of Skeletal Changes

Case no.	Periosteum		Subperiosteal bone			Cortex			Joint lesions		
	Dual layers	Periostitis	Active bone formation	Lamination of new bone	Inactive new bone sheath	Cortical and periosteal layers fused	Osteoporosis of cortex	Bone proliferation in tendon	Synovitis	Degenerative changes in cartilage	Pannus
1	+	−	+	−	−	+	+	+	−	−	−
2	+	+	+	+	−	+	+	+	+	+	−
3	−	−	−	−	−	−	+	+	+	+	−
4	+	+	+	−	+	−	−	−	+	No cartilage studied	−
5	+	+	+	+	+	+	+	+	+	+	+
6	+	+	−	−	−	−	−	−	+	−	−
7	+	+	−	−	−	−	+	−	+	±	−

After the new periosteal bone is fully developed and calcified, numerous osteoclasts may be noted upon the now buried surface of the cortex and within the spaces of the haversian systems as well. Focal bone resorption produces bay-like surface irregularities which, after considerable enlargement, are filled with fatty marrow. Some of these become continuous with the enlarged marrow spaces in the subperiosteal bone sheath. Distinction between the original cortex and the layer of new bone is thus further obscured. Continuation of this resorptive trend results ultimately in similar cancellous structure in both periosteal and cortical bone. The shaft, therefore, is markedly thickened but spongy in character. Crump [7] and Janeway [9] observed concomitant resorptive activity upon the endosteal side of the cortex which they stated eventually caused an increase in the diameter of the

original marrow cavity. In the present cases, however, there was no evidence of either endosteal resorption or widening of the medullary space.

Joints

Six of the 7 patients complained of symptoms suggesting involvement of the articulations (Table I). The tissues removed from the interphalangeal joints of one subject (case 3), from whom no such symptoms were elicited, revealed chronic inflammatory changes in the synovia and well marked degenerative lesions in the articular cartilage (Table II). Of the 6 patients presenting clinical signs of arthritis, only one (case 1) failed to show pathologic changes in the articular tissues. Failure to demonstrate microscopic evidence of joint disease in this instance may have been due to the fact that only a portion of one astragalotibial joint and one interphalangeal articulation were removed for study.

In the 2 patients from whom the most representative specimens were removed (cases 2 and 5), pathologic examination revealed chronic synovitis and degenerative lesions in the articular cartilage surfaces (Figs. 16, 17, 19, 21, and 22). Pannus covering a portion of the patella was observed also in one of the knee joints (Fig. 20).

A specimen of synovia and articular capsule excised surgically from the knee of one patient (case 4) revealed, in addition to pronounced edema (Fig. 15), a moderate degree of chronic inflammation of the subsynovial tissues. Marked thickening of the walls of small and medium-sized blood vessels with occasional thrombosis was observed also (Fig. 18).

In case 6 the examination of articular structures was limited to the interphalangeal joints of one thumb. Slight diffuse lymphocytic infiltration in the synovial tissues and hyperemia were the only abnormalities observed.

From these observations it is apparent that the pathologic changes in the joints of patients with hypertrophic osteoarthropathy are varied in both severity and kind. It appears, however, that edema of the subsynovial tissue and the accompanying diffuse infiltration with lymphocytes and plasma cells comprise the most constant morphologic abnormalities. In the more markedly affected joints the infiltrating cells tend to accumulate in the perivascular areas of the subsynovial layer. These changes, which seem to occur concomitantly with the inflammatory reaction in the periosteal tissues adjacent to the articulations, sometimes are accompanied by moderate proliferative activity in the synovial membrane, leading to villous hypertrophy or, in rare instances, to the spread of pannus on the articular surface.

The same tendency to thickening of arterial walls through medial hypertrophy and subintimal proliferation that is frequently present in the periosteum may be found also in blood vessels of the articular capsule. The alterations observed in the surfaces of the articular cartilages are, for the most part, similar to those seen in degenerative joint disease.[10] Pallor of the cartilage matrix, accompanied in the more severely altered joints by fibrillation, often is evident. The free edge of the articular surface may be pitted, uneven, and the total thickness of the cartilage layer diminished. Focal resorption of subchondral bone trabeculae is observed frequently and a number of osteoclasts usually are present in these regions. Such resorption appears to be more marked in patients with generalized hypertrophic osteoarthropathy than would be expected with degenerative joint disease in those of comparable age. The extension of vascularized tufts of fibrous tissue into or through the calcified layer of subarticular cartilage noted in some specimens (Fig. 21) may lead to focal areas of resorption in the joint cartilage itself (Fig. 22). It is probable that these changes lead to an accelerated degenerative process in the superficial layer of the articular cartilage.

Clubbed Digits

All of the patients in the present series showed digital clubbing on physical examination. In the 5 patients from whom roentgenograms were available it was noted that the bulbous enlargement of the fingers and toes was due chiefly to alterations in the soft tissues. Roentgenograms of the hands of one patient (case 1) showed a few spur-like overgrowths of bone from the cortex of some of the terminal phalanges (Fig. 1). Specimens were obtained from the fingers and toes of 5 patients (Table I).

From the study of this material it is evident that the changes responsible for clubbing may be found exclusively or in large part in soft tissue layers. The collagen bundles in the corium appear swollen and there is widening of the interfascicular spaces. Enlargement of the rete pegs in association with narrowing of the epidermal papillae also may be present. Lymphocytic and plasma cell infiltration in the extra-osseous tissues, in a manner similar to that observed in the extraperiosteal connective tissues elsewhere, is present and may be more marked near the distal ends of the digits.

The walls of small and medium-sized arteries external to the periosteum frequently are thickened. This is due in great measure to hypertrophy of the medial layer, although subintimal thickening and

fibrosis also may be present. The caliber of the lumina of such vessels may be significantly diminished.

The periosteum of the terminal phalanges shows relatively little change when compared with other portions of the skeleton. The most constant change consists of a division of this layer into an outer fibrous and an inner cellular cambial zone. Slight or moderate lymphocytic infiltration may be present in the former. Sections of metacarpals or proximal phalanges of the digits showing minimal periosteal changes in the terminal phalanges may reveal well marked new subperiosteal bone formation.

Among the present specimens there was one in which several irregular deposits of osteoid matrix had occurred within the marrow cavity of a terminal phalanx. The cause of this unique lesion was not apparent. Another digit showed an incompletely calcified bony excrescence within a tendon at the site of its insertion into bone. This lesion was presumed to be representative of those giving rise to the spur-like bony overgrowths visible in the roentgenograms (Fig. 1). Microscopically, it was similar to the bony overgrowths occurring at tendon insertions in degenerative joint disease.[10]

Discussion

Marie [3] and Bamberger [2] first described the widely distributed osseous changes in the syndrome now known as generalized hypertrophic osteoarthropathy and established the process as a clinical entity. Digital clubbing, although long recognized, had not been related to generalized skeletal disease. It is quite universally agreed at the present time that enlargement of the acral parts, subperiosteal bony overgrowth, and joint lesions, when present, are all related manifestations of a single syndrome.[4-6,9,11,12]

In the majority of instances these peripheral changes follow a primary pulmonary disease which is either initially or secondarily of an inflammatory nature. Pulmonary tuberculosis, bronchiectasis, severe emphysema, primary or metastatic neoplasm of the lung or mediastinum, and suppurative lesions of the lung or pleura are the more common exciting conditions. Diseases of the heart, especially those of congenital origin and long-standing valvular lesions, also lead to the development of the syndrome. In addition, a number of extrathoracic conditions, notably pyelonephritis, dysentery, syphilis, alcoholism, chronic intoxication with phosphorus or arsenic, jaundice, and biliary cirrhosis have been held responsible.[4,13]

The syndrome is known to be more common before middle life and

to affect males much more frequently than females. A congenital form of digital clubbing also has been recognized but this condition differs from the secondary syndrome in that there are no associated changes in the long bones, and related joint symptoms are absent. A further dissimilarity has been indicated by the studies of Mendlowitz [14] who found evidence of increased blood flow in the finger-tips in patients with all types of clubbing except the hereditary form.

The local factors concerned with the development of hypertrophic osteoarthropathy remain obscure although numerous hypotheses have been ventured. Bamberger [2] attributed the condition to a circulating toxin derived from the underlying suppurative disease, but considered the possibility that the osseous changes might result also from the therapeutic use of such chemical agents as phosphorus or arsenic. Marie [3] believed that irritative toxins elaborated by the decomposition of static secretions in bronchiectatic cavities were responsible. More recent observers, impressed by the great frequency with which osteoarthropathy is associated with pulmonary tuberculosis or other chronic pulmonary infections, have adopted the "toxic" theses of Marie and Bamberger. Mauer [15] has introduced the interesting concept of alteration in red cell suspension stability which, despite accelerated acral blood flow, leads to peripheral arterial anoxia. The presence of increased peripheral vascular flow is attested by the studies of Charr and Swenson [16] and by Mendlowitz.[14]

The occurrence of the syndrome in patients with congenital heart disease in whom no infectious lesions are demonstrable has led other observers to the belief that imperfect blood oxygenation resulting from either defective intrapulmonary aeration or impedition of vascular outflow from the lungs is the responsible disturbance. It has been suggested also that interference with circulatory function, due either to pulmonary or to cardiac lesions, may act in combination with toxins produced by associated infectious processes to produce the syndrome.[11,17] Because of the symmetric distribution of the skeletal changes, the possibility of neurogenic factors also has been considered.[5,18] In several instances the process has been thought to be the result of disordered endocrine function.[19]

It is clearly evident that these theories have given no precise explanation for the mechanism underlying the varied skeletal and soft tissue lesions of the syndrome. It appears probable that real progress toward the solution of the problem of etiology must await the development of an improved method whereby the lesions can be produced experimentally. Since the disease is reported as a relatively frequent spontaneous

occurrence in the dog,[20] an experimental method would seem to be available.[21]

The physical signs and the symptoms leading to the clinical recognition of hypertrophic osteoarthropathy are extremely varied.[5,17,22] In the majority of cases widening of the terminal portions of the fingers and toes, with or without excessive curvature of the nails, is the first abnormality noted. Many patients, however, complain of intermittent pain and tenderness along the extremities. Stiffness and tenderness elicited by movement of the peripheral joints frequently are noted.[5,8,12,22,23] Occasionally advanced periosteal lesions may be visible in the roentgenogram before the condition is suspected by either patient or physician. Not uncommonly, signs and symptoms pointing to the presence of the skeletal changes may antedate those referable to the primary visceral disease.[24]

The anatomical findings aid one in explaining the varied clinical manifestations. The enlargement of the fingers and toes is due to an increase in the bulk of the soft tissues around the terminal phalanges and beneath the nails. Although some uncertainty prevails concerning the exact nature of this soft tissue change and its relationship to the ossifying process elsewhere in the skeleton, it is apparent that hyperemia, edema, increased amounts of loosely textured connective tissue, and mild chronic inflammation are the predominant features of the lesion.[5,12,22,25-28] All tissue layers from the epidermis inward to the periosteum may be affected in varying degree, the most marked change occurring in the terminal portions of the digits. It is not surprising, therefore, that clubbing may develop within relatively short periods of time or regress promptly during remissions of the underlying visceral disease.[6,24] Bony overgrowth leading to "spurring" or "mushrooming" of the terminal phalanges occasionally develops in the more severely affected patients. Such osseous lesions develop in previously enlarged digits and thus contribute little to the acral deformity. In children the amount of soft tissue swelling may be such that the terminal phalanx may undergo pressure atrophy.[29]

The osseous lesion begins as a low-grade inflammatory reaction in the periosteum. This is followed by a remarkable degree of subperiosteal new bone formation with centrifugal displacement of the thickened periosteum. These changes may occur fairly rapidly and may thus induce pain and tenderness. Slowly progressive or quiescent lesions tend to be asymptomatic.

The periosteal changes usually are observed first along the distal third of the bones of the forearm and leg. Progression, although very

irregular, is usually toward the proximal portions of these bones. At a later stage similar lesions appear along the lower ends of the femur and humerus (Fig. 4). Still later there may be involvement of the shafts of the metacarpals and metatarsals and less frequently of the proximal and middle phalanges. The changes usually are bilaterally symmetric. There is a tendency for the process to be more marked on the dorsal and medial surfaces although pronounced lesions are especially likely to develop in areas where tendons insert.[7,8,30] The productive changes beneath the periosteum diminish near the expanded ends of the diaphyses and rarely are present in areas covered by articular capsules (Figs. 2 and 3). Although microscopic alterations are frequent in the terminal phalanges and in the tarsal and carpal bones, lesions distinguishable by clinical or roentgenographic examination rarely are observed in these areas.[5,12,22,31] In addition to the predilective sites of bony overgrowth noted in the present study, lesions have been described by others in the clavicle, scapula, patella, and iliac crests, and enlargements of the nose and malar prominences have been recorded.[22,27,28,31,32]

It has been noted in the present study that certain portions of the skeleton may show rapidly progressing periosteal lesions while in other areas in the same patient the process is stationary or undergoing resolution. These differences in activity afford an explanation for some of the observed variations in symptoms and also suggest that certain purely local factors must play a part.

Although the pathologic changes in articular structures often are slight in comparison with those in the neighboring periosteum, there are certain similarities in the reactions. Edema and mild chronic inflammation of the synovia and inner portions of the articular capsules are the most constant changes in painful joints. These have their counterparts, varying only in degree, in the periosteal process. The character of the synovitis, however, differs in no significant manner from that noted in other forms of painful articular disease. It appears probable, therefore, that the symptoms of joint pain and stiffness are caused chiefly by the arthritis associated with secondary osteoarthropathy and are not necessarily to be attributed, as some observers have suggested,[30] solely to the adjacent periostitis. There is little doubt, however, that the periosteal changes frequently are responsible for some of the symptoms which are considered both subjectively and objectively to have origin in the joint.

Proliferative and inflammatory changes in the synovial tissues of a degree sufficient to cause ankylosis are observed rarely. However, as shown in our case 5, pannus may develop occasionally and lead to ad-

hesions across the joint space. The actual relationship of the degenerative changes in the articular cartilage to hypertrophic osteoarthropathy is not altogether clear in the present study. The only microscopic difference between such degenerative lesions in our patients and in otherwise healthy persons of comparable age is the presence of resorptive changes in the subchondral bone and the penetration of vascularized tufts of marrow tissue into or through the calcified layer of cartilage. It is possible that this may be nothing more than a result of atrophy of disuse.

Summary and Conclusions

A pathogenetic pattern has been developed on the basis of a detailed study of the skeletal lesions of generalized hypertrophic osteoarthropathy as observed in 7 cases.

The most striking finding consisted of a productive periostitis involving the long bones of the extremities. In this location the process showed variously an inflammatory periostitis characterized by lymphocytic and plasma cell infiltration, subperiosteal new bone formation, and the production of a pseudo-cortex which ultimately fused and expanded the original cortex. There was evidence to suggest intermittent activity of the periosteal lesion.

During the course of fusion of the original cortex and the newly formed subperiosteal bony sheath, the former exhibited resorption and adaptation to increased shaft diameter.

Articulations in involved extremities were the seat of mild to moderately severe chronic synovitis associated with non-specific degenerative changes in the articular cartilages.

Clubbing of the digits appeared to result from an increase of soft tissue bulk and was associated with few or no morphologic changes in the terminal phalanges.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 61

FIG. 1. A roentgenogram of the hands in case 1. Expansion of the soft parts of the finger-tips is evident and there is pronounced spurring of the terminal phalanges. Save for isolated points, presumably of tendon insertion, there is no detectable periosteal reaction.

FIG. 2. A roentgenogram of the ankles in case 5. The periosteum of the tibia and fibula is thickened and calcified. The process is more marked over the medial aspect of the bones.

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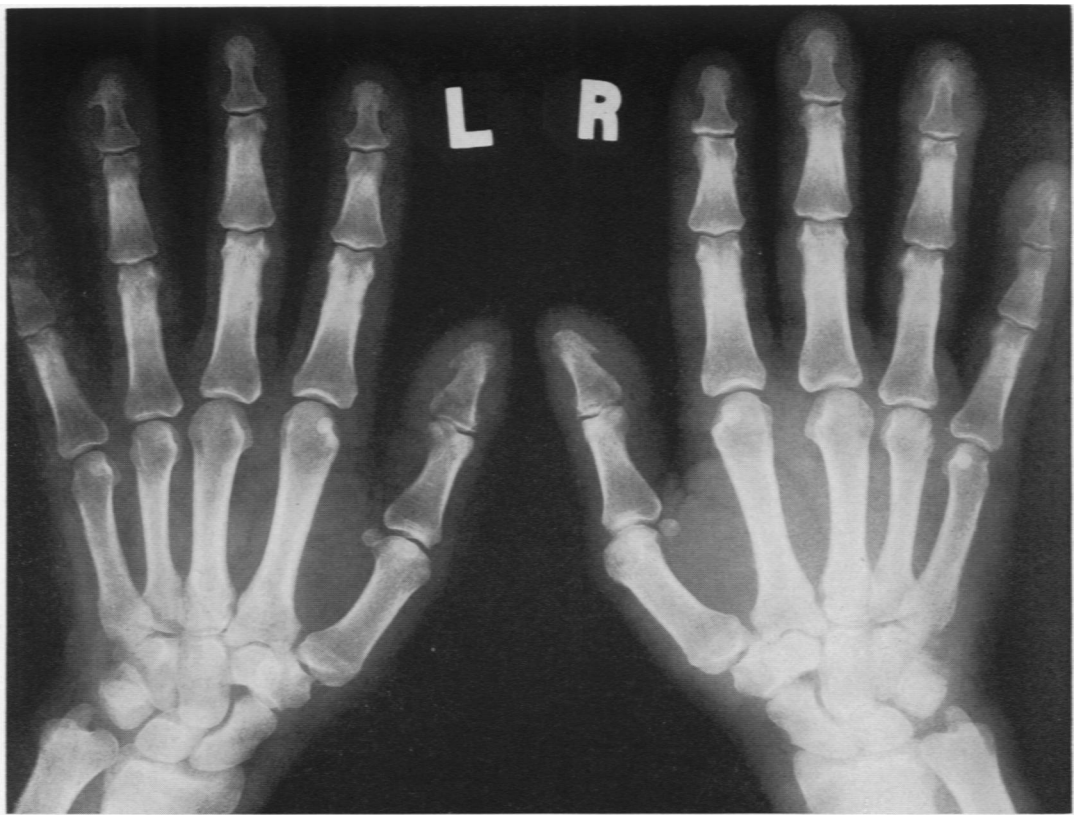

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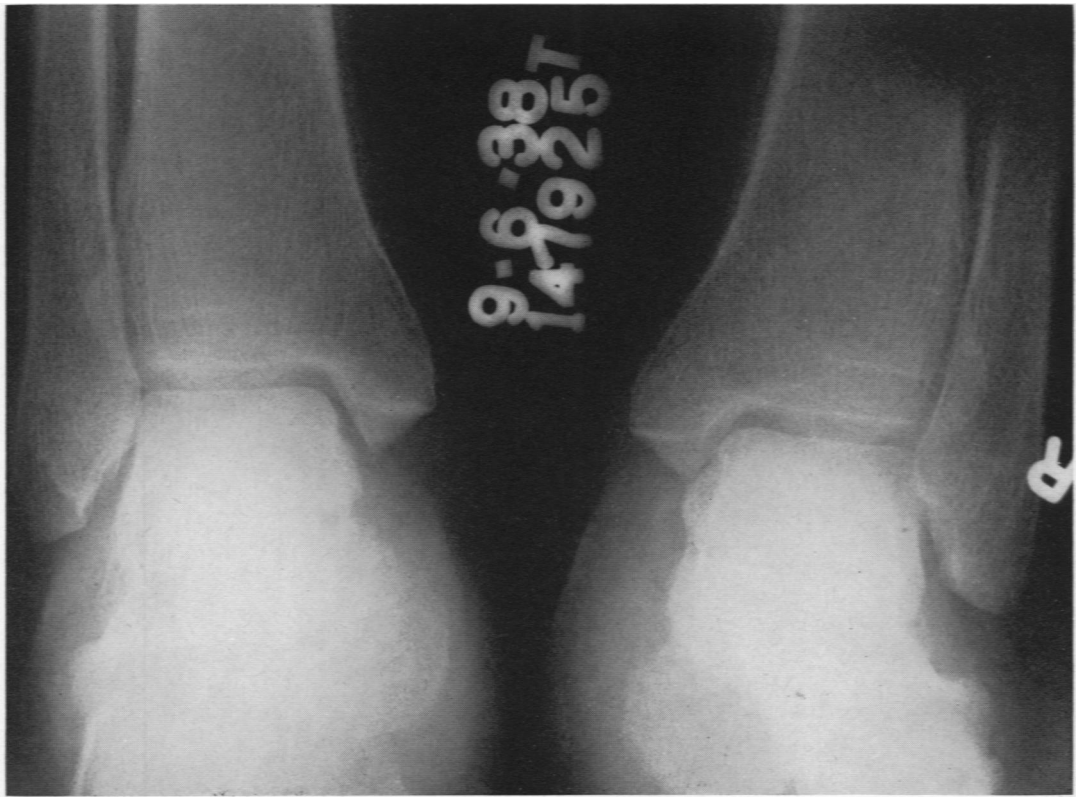
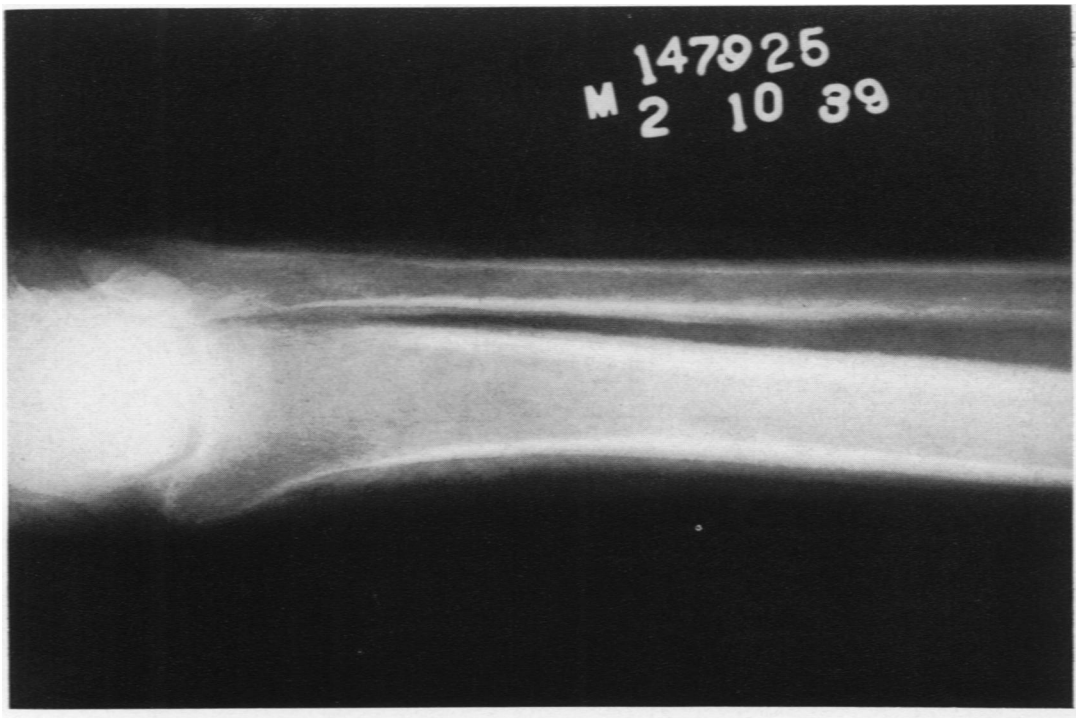


PLATE 62

FIG. 3. A roentgenogram of the left leg in case 5, taken 5 months after that shown in Figure 2. The periosteal lesion extends well up the shafts of the tibia and fibula and is now thicker and more mottled than previously. The predilection for the medial sides of the bones again is apparent.

FIG. 4. A roentgenogram of a knee in case 5. The joint and upper portions of the tibia and fibula reveal only minimal changes. A marked subperiosteal overgrowth of bone upon the femoral shaft is apparent.



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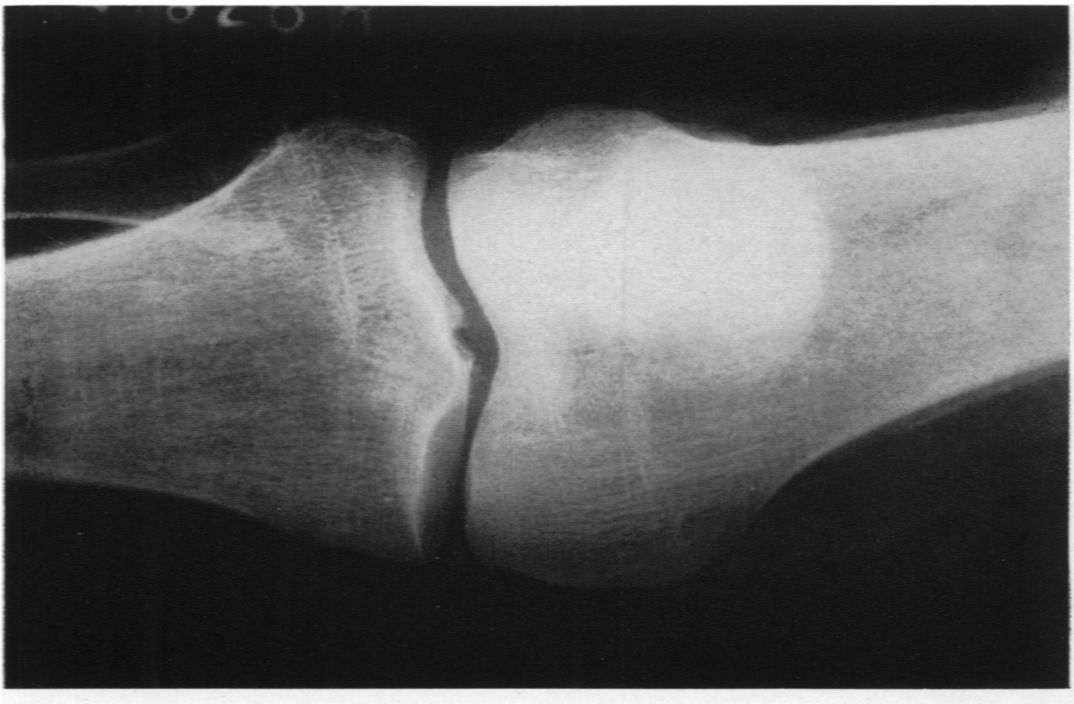

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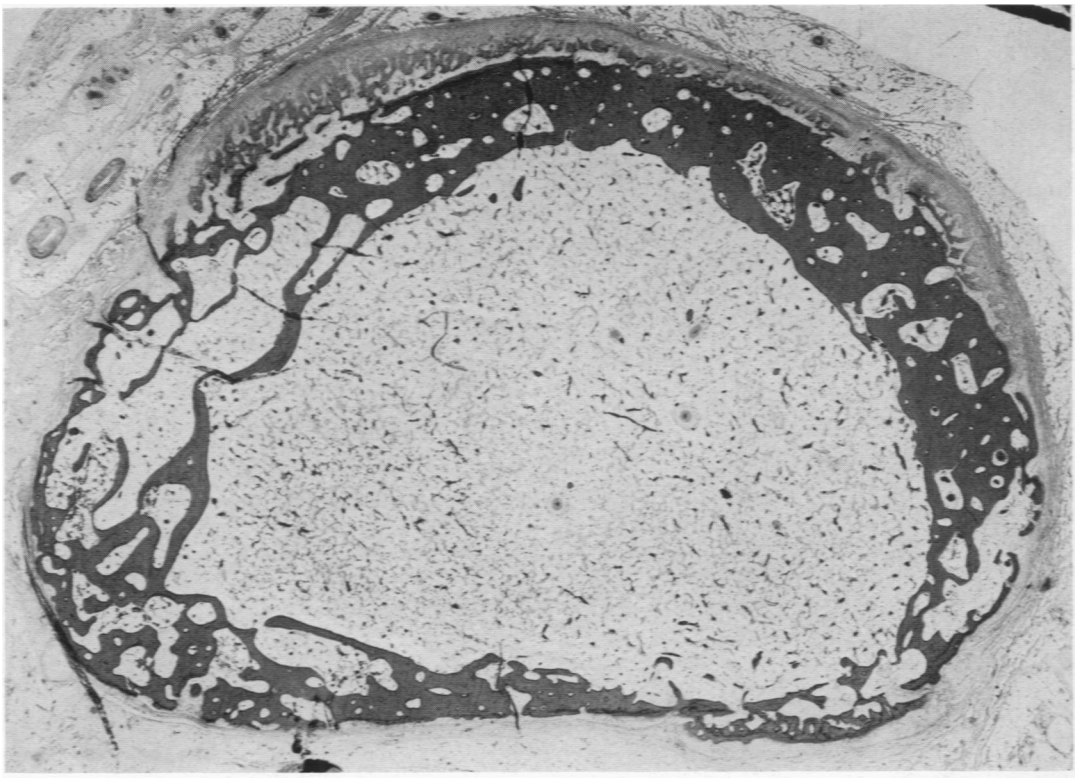
PLATE 63

FIG. 5. A cross section through a metatarsal in case 5. The periosteum on the dorsal and medial aspects is thickened and divided into an outer fibrous and an inner cambial layer. There is an irregular deposit of new bone upon the cortex. The latter shows considerable osteoporosis. × 11.

FIG. 6. Specimen taken for biopsy from the periosteal surface of the lower end of the femur in case 5. The fibrous periosteum is dual layered and the outer coat contains an inflammatory reaction. Subperiosteal trabeculae are still arranged perpendicularly to the periosteum. Short rows of osteoblasts affixed to the trabeculae have caused a deposit of thin osteoid seams. Marrow tissue within the newly formed bone is edematous, fibrillar, and vascular. × 56.



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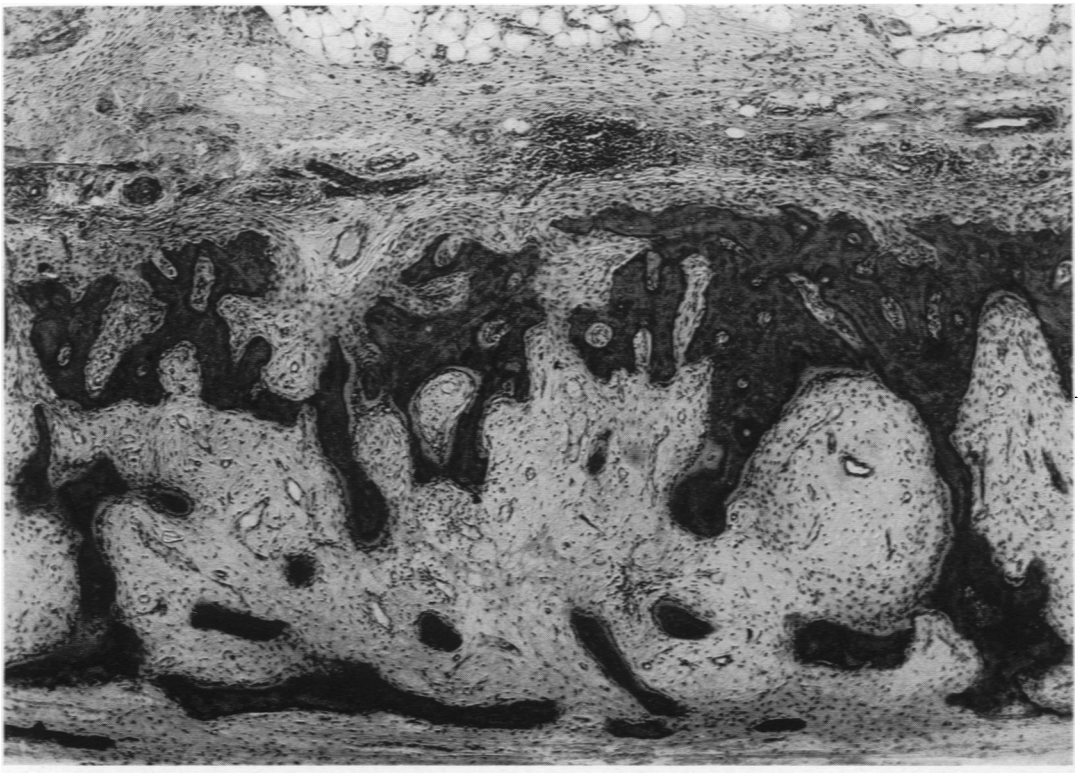

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PLATE 64

FIG. 7. A cross section through the wall of the femur in case 5. The columns of new bone are arranged in palisade fashion. Ossification is more advanced in the deeper portions. The point of fusion with the cortex is manifested by a densely staining but broken cement line. Blood vessels entering from the periosteal layer are perpendicularly placed and form a series of arcades. × 11.

FIG. 8. A higher power view from the same section as that used for Figure 7. The periosteum is dual layered and contains a marked round cell infiltration within its outer zone. The columns of osteoid are calcified in their deeper reaches. The tissue intervening between the trabeculae is fibrocellular. One of the penetrating blood vessels is apparent. × 56.

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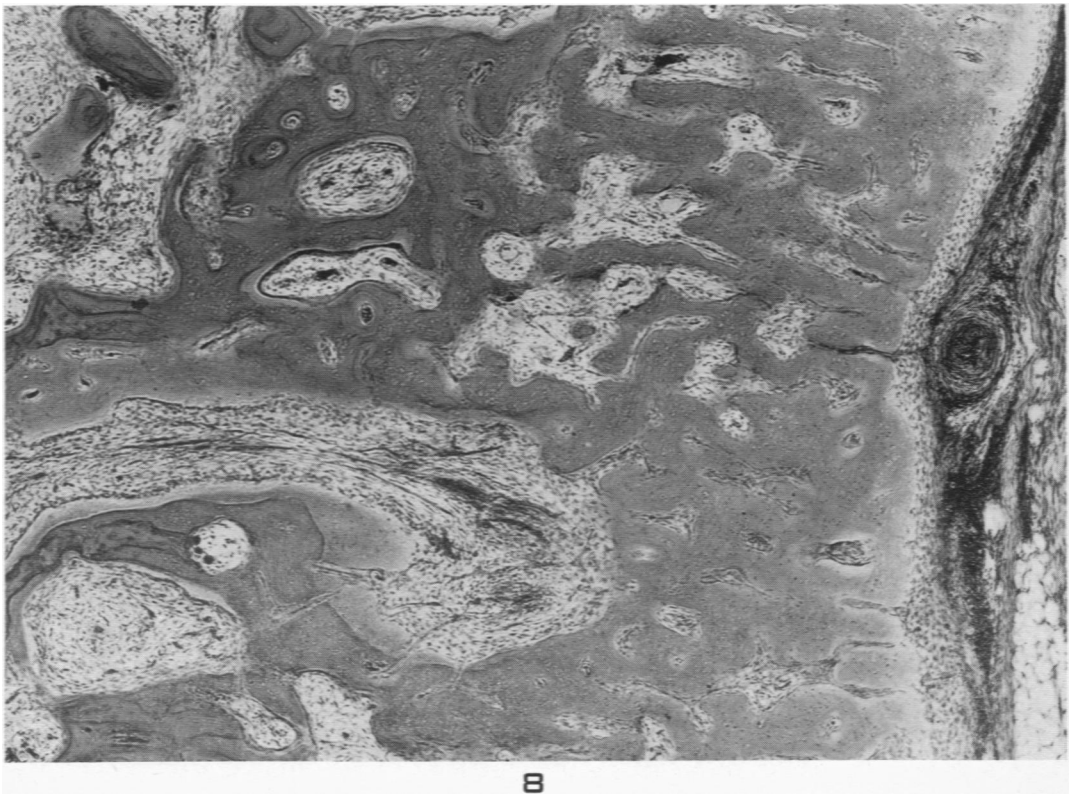

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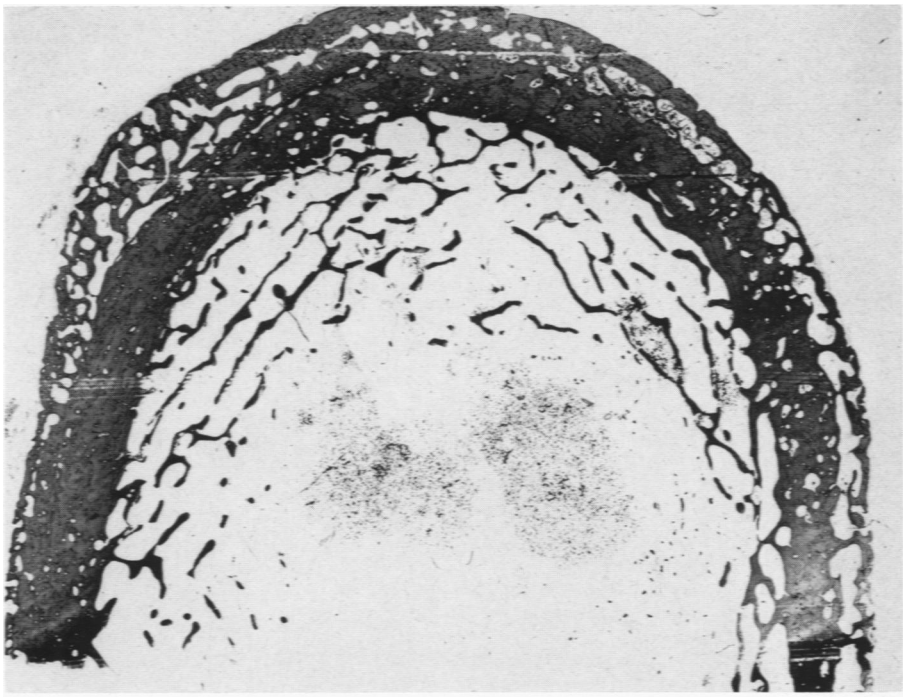
PLATE 65

FIG. 9. A cross section of the tibia in case 2. There is no evidence of osteogenic activity at this time. The bone previously deposited has formed a cancellous sheath about the old cortex which now shows foci of lacunar resorption. The radial appearance of the trabeculae has disappeared and a well defined pseudo-cortex has been formed. × 2.

FIG. 10. A cross section of the fibula in case 5. Apparent transient arrest in activity with completed mineralization has permitted ensheathment of the shaft by a thick layer of cancellous bone. Early lacunar resorption in the original cortex has begun to obscure distinction between the two layers. Evident reactivation of the process has produced a new layer of osteoid superimposed upon the pseudo-cortex with resultant lamination. × 13.



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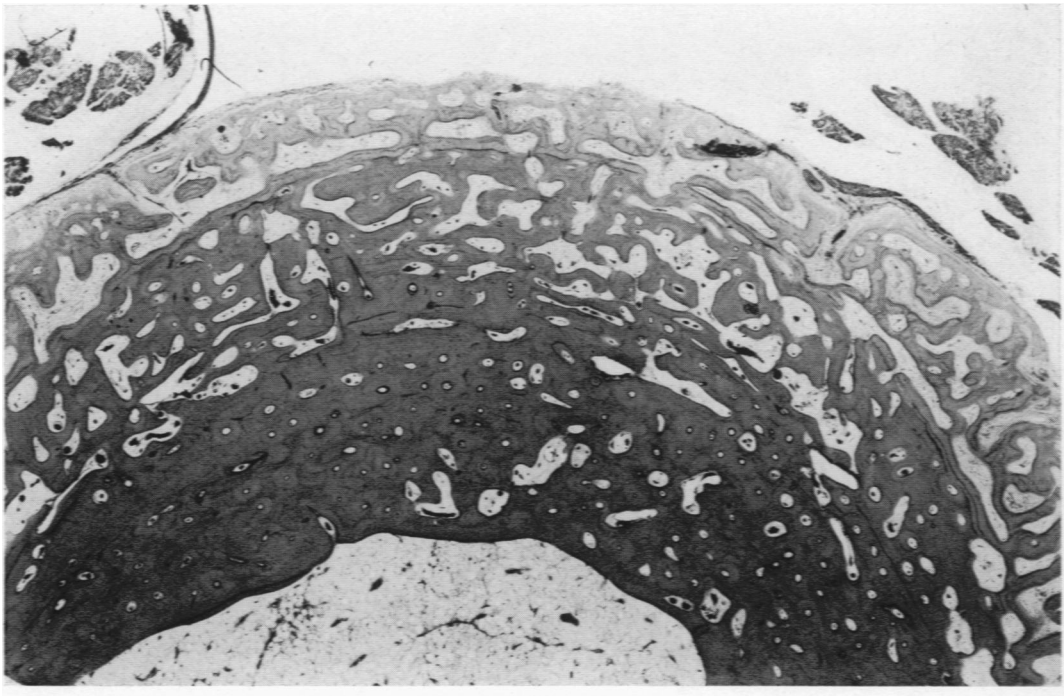

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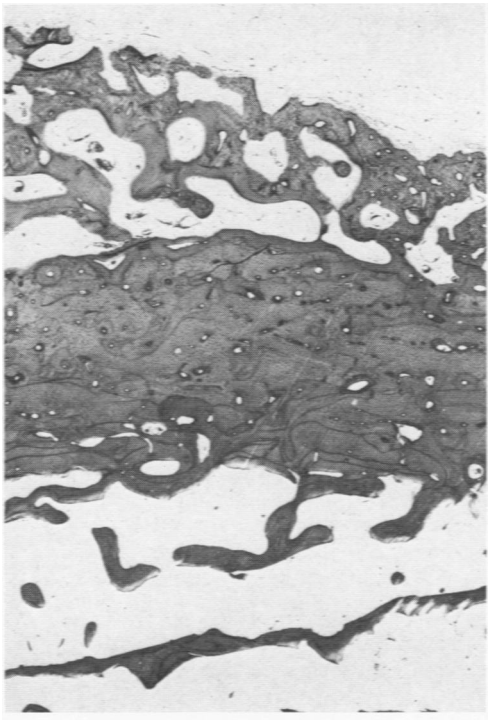
PLATE 66

FIG. 11. A higher power view of the section shown in Figure 9. Fusion of the cancellous sheath and old cortex as well as the formation of a pseudo-cortex is apparent. × 13.

FIG. 12. A longitudinal section from the tibia in case 1. Lacunar resorption of the outer portion of the true cortex has caused it to become as cancellous as the subperiosteal sheath. It is difficult to distinguish between the newly formed and the original cortical bone. There is no evidence of resorption from the endosteal side. × 13.

FIG. 13. A tendon attachment on the femur of case 2. Irregular masses of osteoid have extended into the substance of the tendon. × 54.



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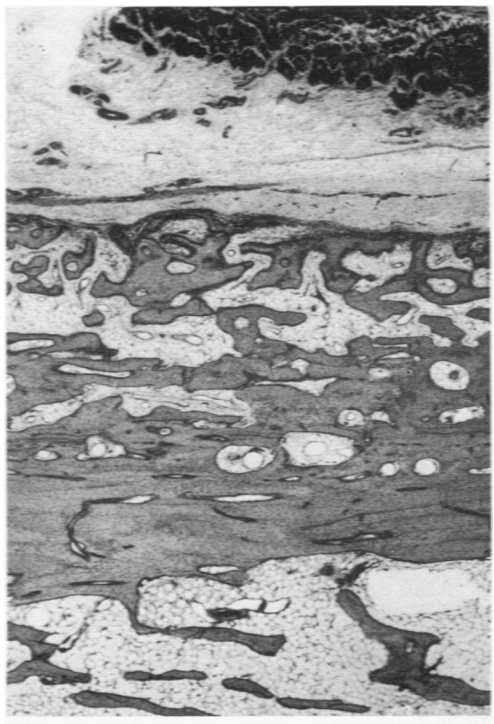

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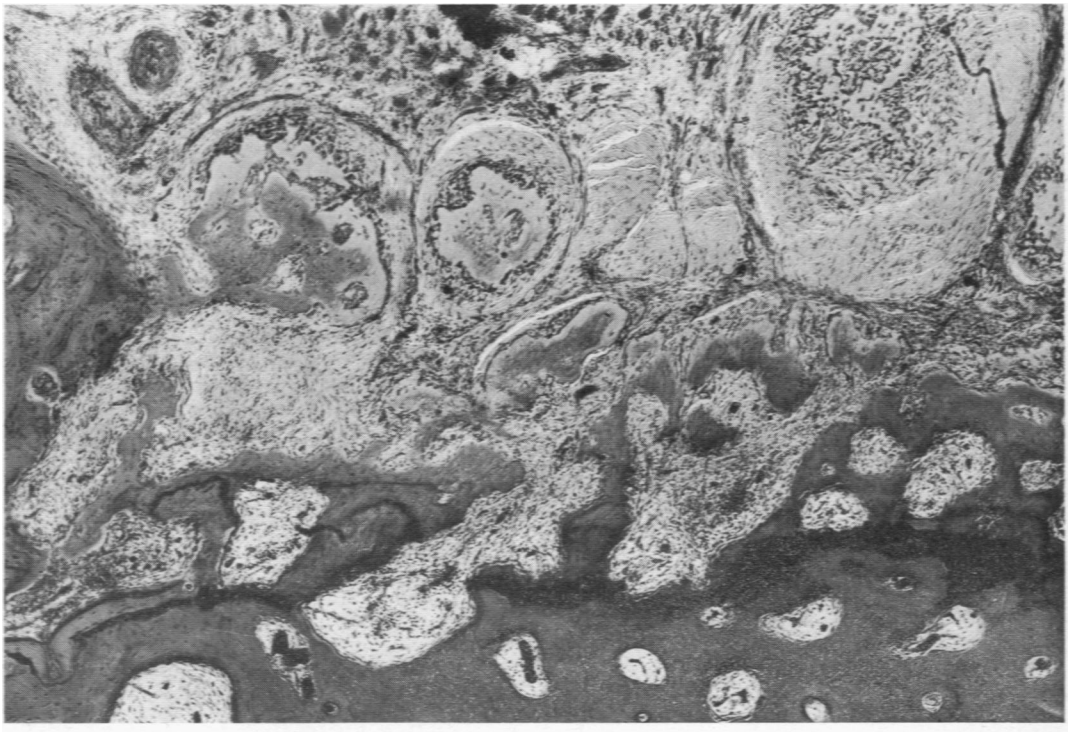

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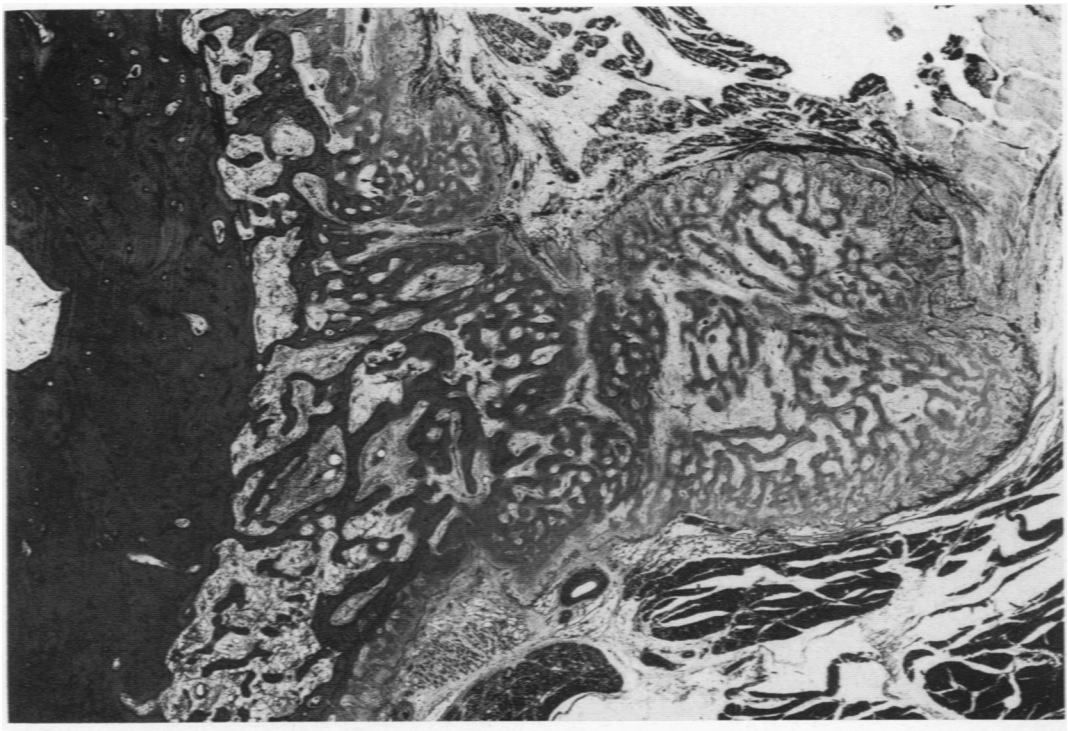
PLATE 67

FIG. 14. A higher power view of one prong of the linea aspera in the lower one-third of the femur of case 5. An exaggerated deposit of osteoid has produced an osteophyte-like structure which is here closely related to the adjacent sheath of periosteal new bone and not to the underlying true cortex. × 13.

FIG. 15. A section of synovial membrane from the knee in case 4. The surface layer is intact but there is considerable edema of the subsynovial tissues. × 110.

FIG. 16. A section of synovial tissue from the knee in case 2. There is edema in the subsynovial layers and lymphocytic infiltration superficially. × 110.



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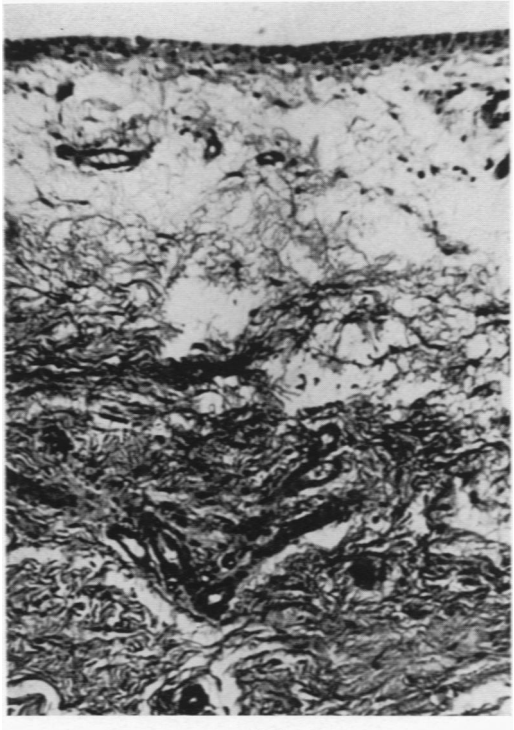

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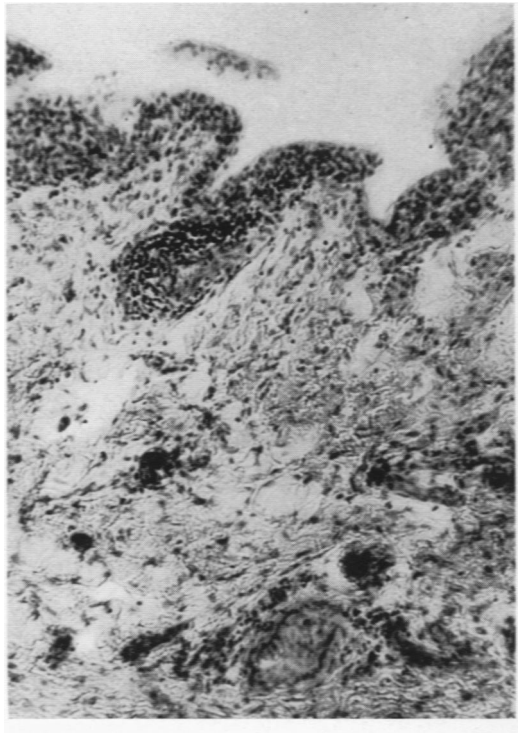

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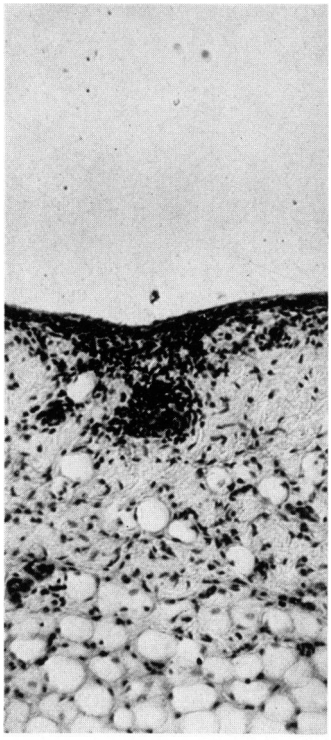
PLATE 68

FIG. 17. A section of synovia from the knee in case 5. Edema and lymphocytic infiltration of the subsynovial tissue are apparent. × 106.

FIG. 18. A section of subsynovial tissue from the knee in case 4. There is scarring with marked fibrous mural thickening of arteries. Arterial lumina are markedly narrowed. × 106.

FIG. 19. A section from the margin of the articular surface of a femoral condyle in case 5. Nests of loose fibrillar tissue and focal areas of bone resorption are present in the subchondral trabeculae and calcified cartilage. × 54.



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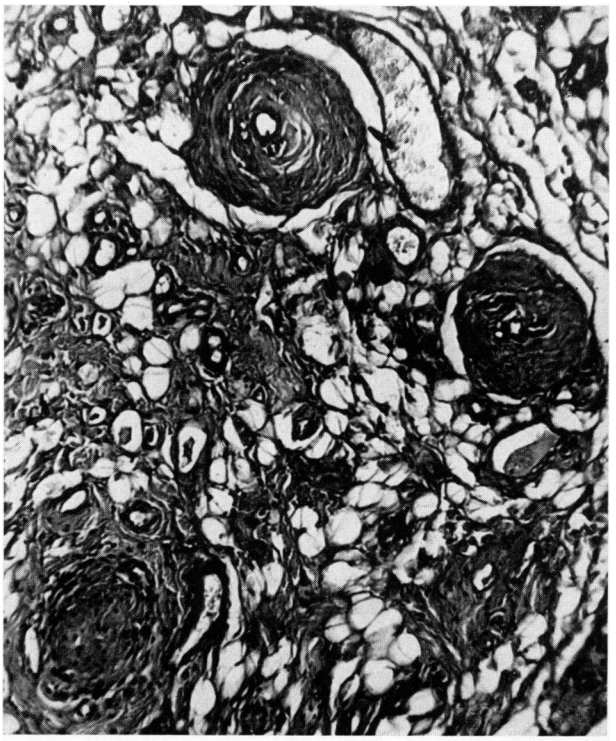

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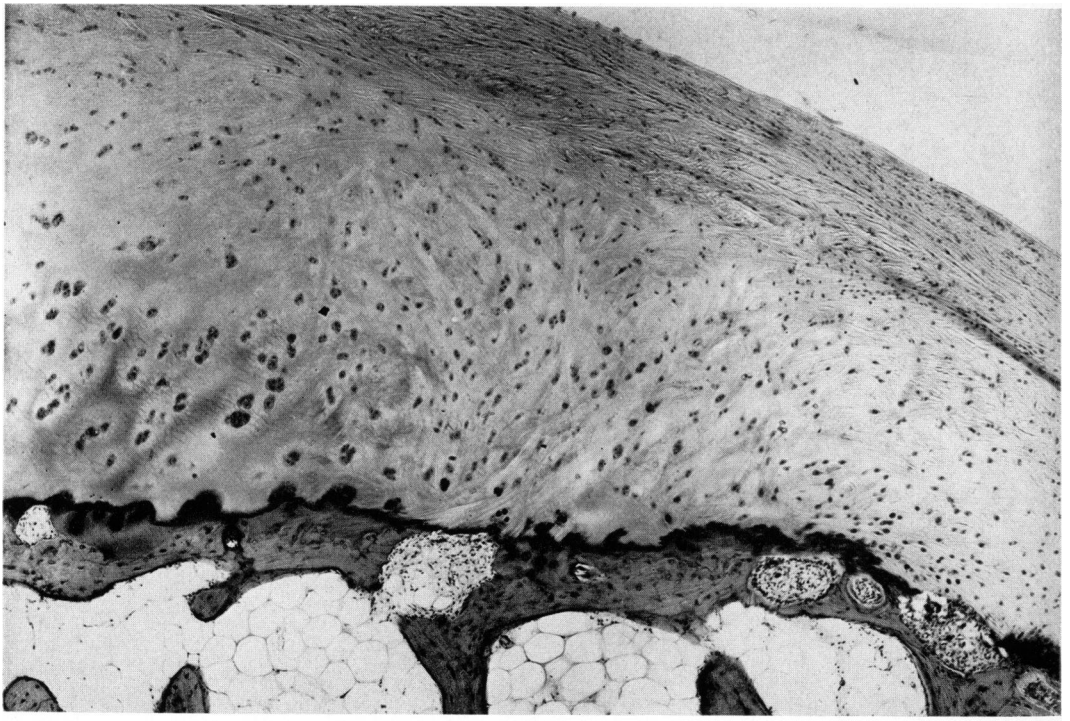

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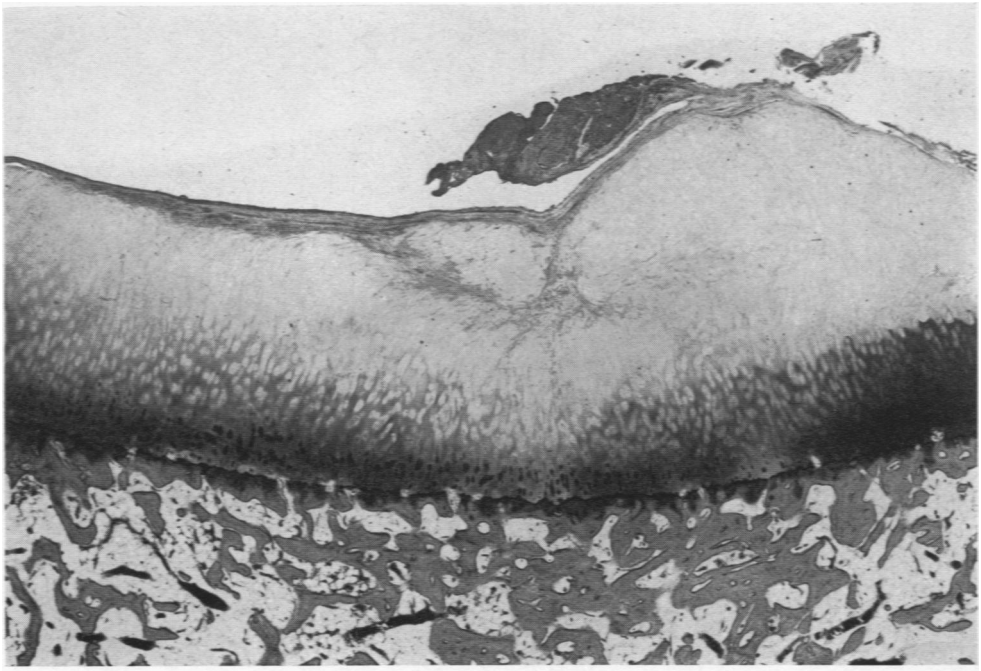
PLATE 69

FIG. 20. A section showing a defect in the patella of case 5. The surface of the cartilage is irregular, eroded, and affixed to it is a thin strand of pannus. × 12.

FIG. 21. Another section from the specimen shown in Figure 20. A large area of cartilage resorption is shown. × 97.

FIG. 22. A section of subchondral plate from the femoral condyle in case 2. A tongue of vascular connective tissue infiltrated with lymphocytes has perforated the bone and is eroding the overlying cartilage matrix. In the latter, lacunar aggregations of degenerated cartilage cells are apparent. × 97.



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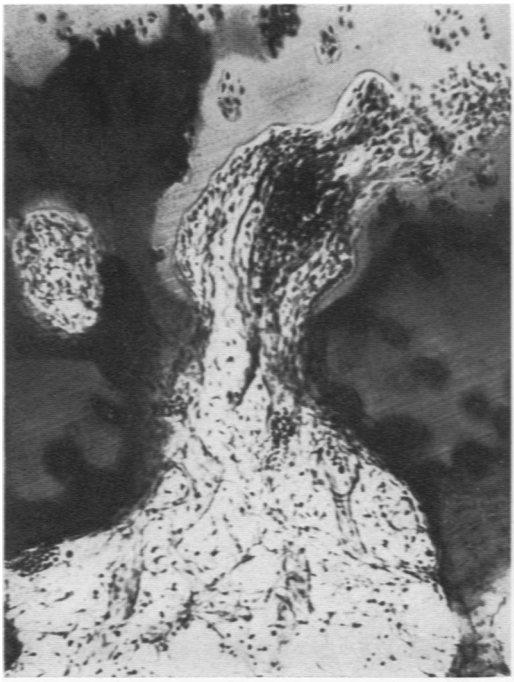

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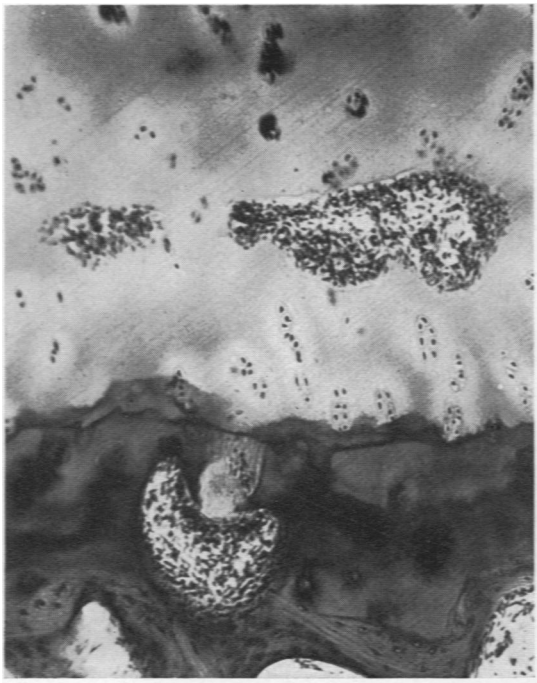

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