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Bone Erosion in Rheumatoid Arthritis†

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A histological study of fully mineralized bone sections was made on thirty joints surgically removed from patients with rheumatoid arthritis. The patterns of bone erosion fell into three groups: 1) that due to multinucleated osteoclasts; 2) areas of apparent bone erosion occupied exclusively by mononuclear cells; and 3) changes produced by an osteocyte which could either enlarge the lacuna space in which it resided or demineralize a region of bone in its immediate vicinity. Tissues taken from knee and hip specimens frequently showed all three cellular patterns of bone erosion, while the sections from finger joints rarely container multinucleated osteoclasts but often revealed mononuclear cells which occupied Howship's resorption lacunae. The presence of mononuclear cells on the bone surface in the earliest as well as the latest stages of erosive rheumatoid arthritis supports the concept that some mononuclear cells have osteoclastic capabilities. Different regions of the same specimen of the larger joints demonstrated low or high cellular activity (both osteoblastic and osteoclastic) which was independent of the degree of joint damage, duration of disease, and drug therapy.

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The significant clinical features of chronic rheumatoid arthritis consist of persistent swelling, pain, discomfort, and decreasing function of many joints. This involvement is usually symmetrical, affecting the small joints of the hands, the wrists, and the elbows, as well as the hips, knees and feet. Less frequently, the cervical spine and temporomadibular joints are affected. At present, the etiology of this nonspecific inflammatory process is unknown. It may spontaneously remit or progress to produce irreparable joint damage. Many aspects of its pathophysiology and response to treatment suggest a basic immunological disturbance. Mechanisms by which damage to bone occur are the subject of this paper.

The earliest bone changes recognizable by x-rays may take six to twelve months to develop. There is first a generalized demineralization and thinning of the trabeculae and cortices near the affected joint, while a more specific type of bone erosion occurs later. With some exceptions, those joints first affected with an inflammatory reaction also tend to develop bone changes first, generally the metacarpophalangeal joints (Figure 1), the wrist, or the metatarsophalangeal joints. Intensity of inflammation, variability of disease activity, and technical factors influence the time interval between the onset of the disease and the appearance of erosions on x-ray. Such factors include the size of the bone or joint involved and the thickness of the surrounding soft tissue; erosions of 1 or 2 mm are easily demonstrated in the fingers and toes while comparable bone defects at the knee, shoulder or hip are difficult to detect. Such technical factors as the number of views taken of the joint, the accuracy of their exposure, the fineness of grain on the x-ray plate, and the diligence of the observer also determine whether the early erosions are identified.

Classically, bone changes represent an extension of the inflammatory reaction of the synovial lining of the joint. They occur earliest where the rim of the articular cartilage becomes continuous with the periosteum of the bone within the joint capsule. Since the inflammatory process affects the soft tissues much earlier than bone, the cells of the synovial lining multiply from the usual one layer of cells to five to ten.

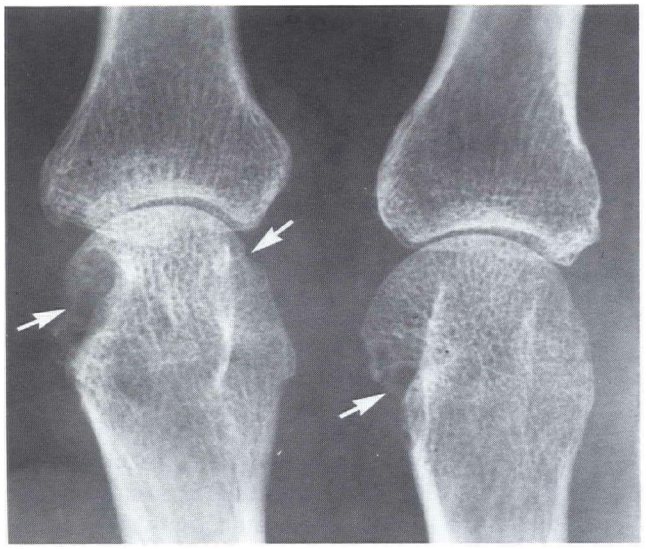

Fig. 1
Bone erosions typical of rheumatoid arthritis, involving two metacarpophalangeal joints.

This proliferation is associated with an increase in vascularity, subsynovial fibrosis, and with the accumulation of round cells, lymphocytes, plasma cells, fibroblasts, macrophages, and polymorphonuclear leucocytes. By a variety of mechanisms,[1-5] the inflammatory tissue, or pannus, then infiltrates and damages the structural components of the joint, including the capsule, tendons, ligaments, cartilage and bone. Numerous biochemical agents are thought to play some role in the destructive process, including lysosomal enzymes, cathepsins, proteases, elastases, collagenases, kinins, and prostaglandins. However, these have little direct influence upon *fully mineralized* bone, which must first be demineralized before it can be attacked by collagenolytic and other inflammatory agents.

Cell populations in bone may be influenced by the inflammation very early in the course of rheumatoid disease before any changes are observable by x-ray.[6-7] Bone biopsies taken at the time of early synovectomy from within the joint capsule but distant from the sites of inflammatory synovitis revealed periosteal erosion of bone with scalloped indentations that resembled Howship's lacunae; these lacunae contained mononuclear cells (periosteocytic fibroblasts) either alone[6] or together with multinucleated osteoclasts.[8] Subcortical inflammation was also present on the endosteal side of the cortex, with adjacent bone marrow fibrosis and inflammation as well as evidence of a local increase in bone turnover.

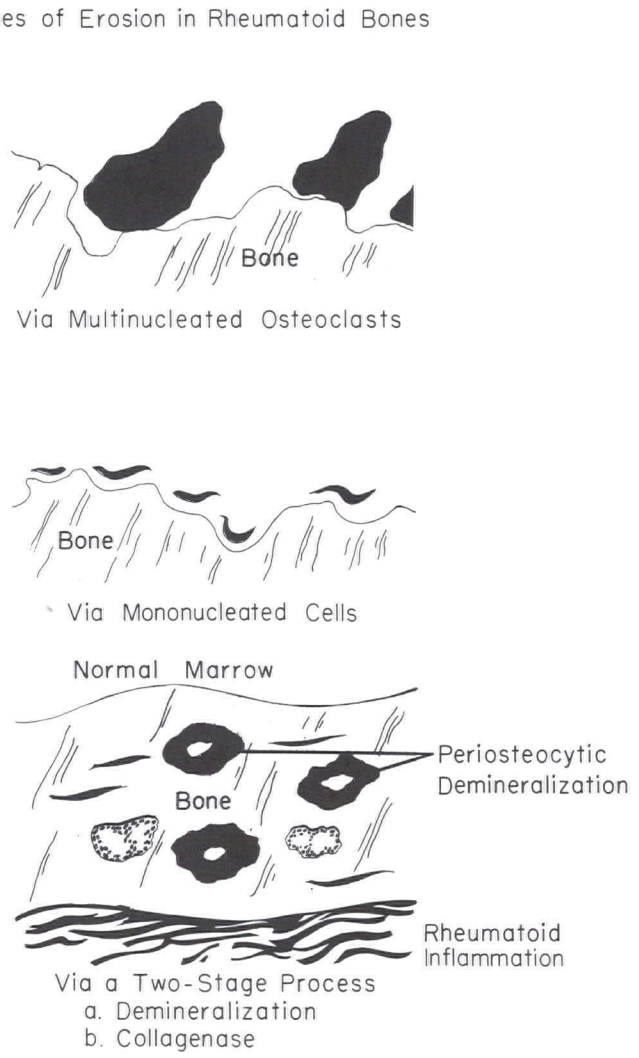

Fig. 2
Schematic representation of mechanisms of bone removal by cellular action.

Material and Methods

We examined thirty joints which had been resected for total joint replacement due to long-standing destructive rheumatoid disease. They included metacarpophalangeal joints, distal ulnar, knees and femoral heads. Specimens were embedded in polymethyl methacrylate and fully mineralized sections were cut 5 to 10 microns in thickness and then stained using the Villanueva bone stain, Goldner's trichrome, Von Kossa and Toluidine Blue. Some sections were demineralized and stained with hematoxylin and eosin (H & E). Sections were also examined with polarized light to distinguish woven bone from lamellar bone. In patients given tetracycline before surgery, sections were examined for tetracycline fluorescence which would indicate new bone formation.

Results

Three main patterns of demineralization and bone erosion were seen in the same specimen of hips and knees, whereas in finger sections often one pattern dominated the whole specimen. Figure 2 illustrates the three major groups: 1) multinucleated osteoclasts; 2) mononuclear cells occupying Howship's lacunae of the eroded bone surface; 3) osteocyte-induced changes, both osteolysis and periosteocytic demineralization.

Osteoclasts

In many areas, numerous osteoclasts were associated with considerable surface irregularity and large lacunae, while small fragments of mineralized bone were surrounded by fibrous tissue and by smaller osteoclasts or extensions from those in contact with the surface (Figure 3). In other sections, the osteoclast occupied a relatively small Howship's lacunae on a flat surface. There were usually fewer than eight nuclei identified in any single cell. In Paget's disease, by contrast, osteoclasts often contain 15 to 20 nuclei in comparable sections. Osteoclasts typically show a distinct preference for mineralized bone, since they may undermine and leave untouched layers of unmineralized osteoid. Occasionally, osteoclasts are seen in contact with cartilage where a subchondral erosion occurs at the cartilage-bone junction in the subchondral plate, at the "tide mark" in H & E sections. This erosion is possibly due to an extension of inflammation along a blood vessel canal as it passes from bone marrow through the subchondral plate,[8] or directly from an extension of inflammatory reaction at the cartilage edge. Multinucleated osteoclasts were rarely seen in finger sections.

Mononuclear cells

In most sections of the finger joints, bone surfaces with undulations resembling Howship's lacunae were frequently

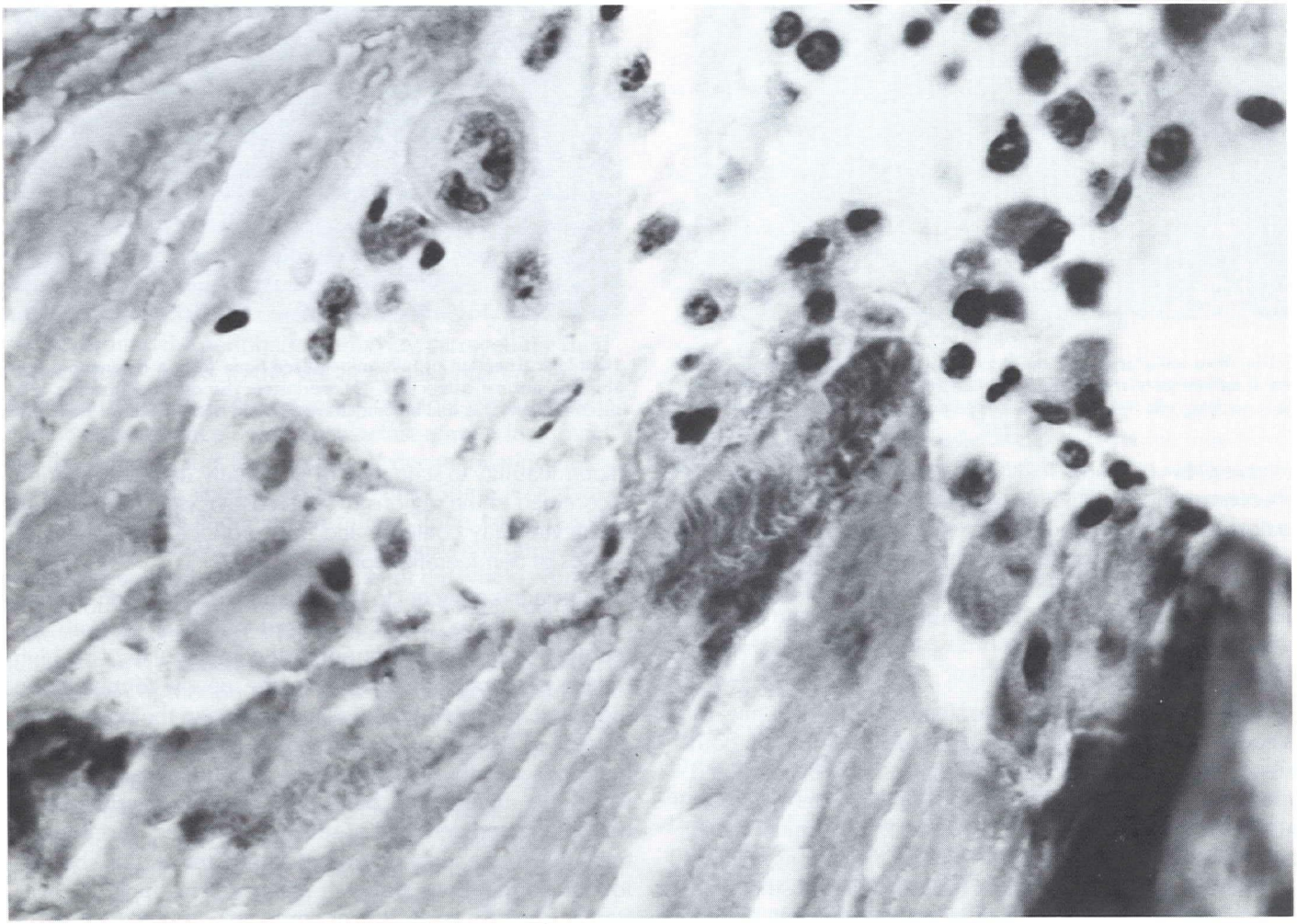

Fig. 3
Multinucleated osteoclasts with some adjacent mononuclear cells in rheumatoid knee (mineralized section, Villanueva Bone Stain x 250).

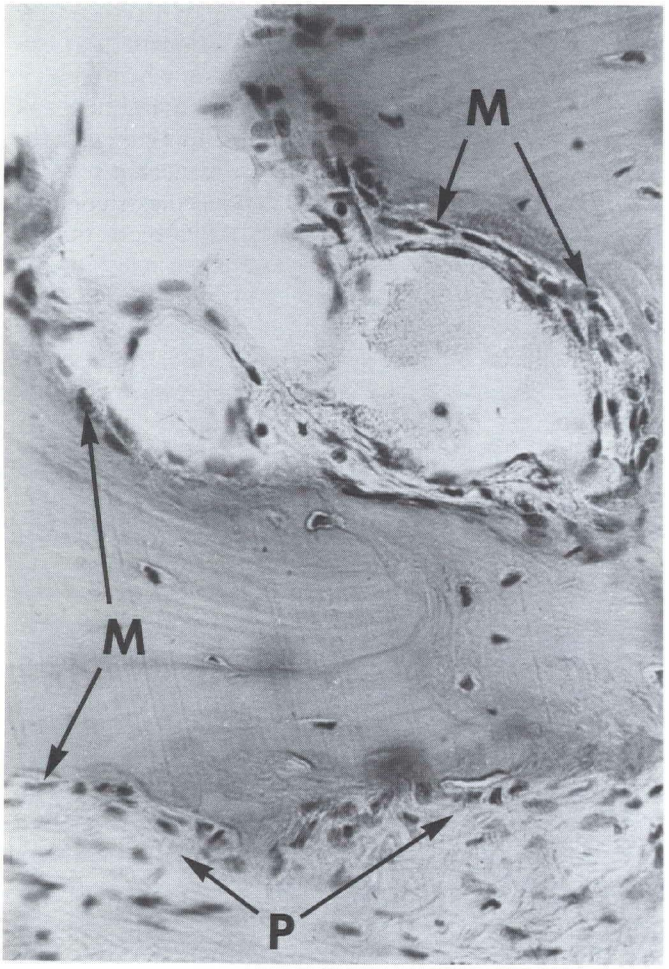

Fig. 4

Section from metacarpophalangeal joint with rheumatoid arthritis. Periosteal surface (P) is irregular and overlaid by fibrous inflammatory tissue. Mononuclear cells (M) occupy scalloped areas of bone surface (H & E x 25).

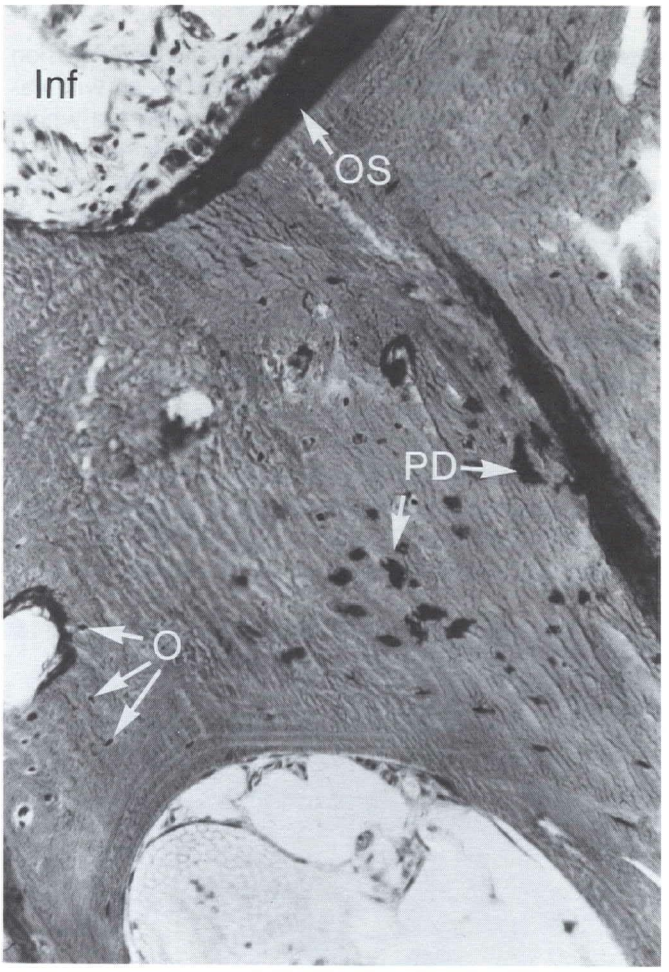

Fig. 5

Histological section of fully mineralized bone from a rheumatoid knee showing normal osteocytes (O), periosteocytic demineralization (PD), osteoid seam (OS), and inflammatory reaction (INF) (Goldner Stain x 16).

occupied by mononuclear cells, some with flat nuclei, others more elliptical (Figure 4). In the larger bones, mononuclear cells were sometimes near multinucleated osteoclasts, but they did not share the same staining properties, and their role as osteoclastic cells capable of further demineralizing was uncertain.

Osteocyte changes

We have noticed enlargement of the osteocyte lacunae, or osteocytic osteolysis, in lamellar bone in joints of both osteoarthritis and rheumatoid patients. A less well identified type of osteocyte reaction, which we have termed *periosteocytic demineralization,* was seen predominantly in rheumatoid disease patients in different locations, within 100 microns of the inflammatory reaction invading the bone surfaces. In this circumstance, whereas the osteocyte lacuna size does not usually change, the area of demineralization next to the osteocyte is increased and identified by the area of permeability to stain (Figure 5). Initially, demineralization is confined to the regions of single osteocytes, yet adjacent osteocytes may coalesce and thus produce larger areas or islands of demineralization.

In some areas adjacent to the inflammatory invasion of bone cortex, we have noted increased numbers of both osteoblasts and osteoclasts lining the trabeculae. The high uptake of tetracycline label by the newly formed bone indicated that this region was very active in the bone repair process as well as in bone removal. This high turnover of bone was usually seen where the inflammation had penetrated the subchondral bone plate and the overlying cartilage had been denuded or severely damaged. By contrast, trabecular bone surfaces in other parts of the section showed low or normal bone turnover patterns. This high turnover staté in specific areas did not correlate with the duration of disease, systemic drug therapy, or with prior injection of corticosteroid into the joint.

Discussion

We observed that the earliest changes noted by Mills[6] and by Muirden[7] may also be found at various stages throughout the whole inflammatory period of the disease, suggesting an episodic or phasic type of cellular involvement. Such a pulsing or episodic pattern has also been suggested by Harris, *et al.*[9] It is well recognized clinically that the joints of some patients will demonstrate a vigorous and continuously eroding pattern that leads to surgery sooner than in other patients with the same duration of disease; in other situations, early erosions may stabilize or even heal. Initial erosions as seen on x-ray occur at the junctions between the synovial tissue and the periosteum, at the junction of the periosteum and the cartilage, and in the "bare area" between these two sites.[10] Why the cartilage and bone junctions are primary sources for erosion is not clear, for cartilage is relatively resistant at least to cellular infiltration and also to biochemical/enzymatic changes unless some prior damage has occurred. On the other hand, the mechanisms of bone destruction and dissolution appear different from that seen in cartilage and soft tissue destruction.

Osteoclasts

These multinucleated cells are responsible for most bone resorption and were noticed in variable and unpredictable numbers in different joints and at different sites in the same joint. It is thought that the osteoclast because of its large size and even larger area of bone erosion is mobile, that its cytoplasm is capable of moving from one site to another, and that the cytoplasm in contact with bone surface "seals" its edges around the periphery. In this way, extracellular fluid does not have access to the site of actual bone erosion or demineralization. It is considered likely that the microvilli on the "active surface" of the osteoclast remain in contact with the mineral and the process of decalcification takes place within this special environment. Some investigators[11,12] believe that demineralization alone takes place, leaving the nonmineral matrix undamaged, while others feel that the osteoclast itself is responsible for the whole eroding process of both the mineral and the collagen matrix.[12] However, collagen fragments have not been identified in multinucleated osteoclast cells, although Harris has identified collagen in mononuclear cells present at the pannus-cartilage junction in rheumatoid arthritis.[9] This suggests that the osteoclast's purpose is to demineralize the surface and to expose the collagen matrix to other cells after the osteoclast moves from that site. The cell which follows is thought to be a mononuclear macrophage with well established collagenolytic capabilities. We have seen numerous associations of osteoclasts and mononuclear cells (Figure 3).

The life cycle and span of osteoclasts is not clearly identified in humans, and their ultimate fate and dissolution have also been a source of debate. Some authors claim that the same nuclei are ultimately converted into mononuclear osteoclasts or modulate to tissue fibroblasts which subsequently may be able to form osteoblasts in an adjacent bone-forming area. Proof of this is still wanting. It is conceivable that at certain periods during inflammatory reactions, fibroblasts, histocytes, precursor cells, or preexisting osteoclasts may be temporarily activated in a pulse fashion, during which time recruitment of nuclei takes place. Such stimulating factors may be either systemic (i.e., drugs) or local, in which products of the inflammation itself may modulate preexisting cells in the bone to develop into osteoclasts. Such factors include "osteoclast activating factor,"[13] prostaglandins,[4] a factor demonstrated by Krane,[15] parathyroid hormone-like materials,[15] vitamin D equivalent, and, more recently, a suggestion from Lindsay, *et al*[14] that an osteoclast stimulant similar to osteoclast activating factor does occur in sera of some patients with rheumatoid arthritis.

Mononuclear cells

The question has often been raised whether mononuclear cells can be osteoclastic, but mononuclear cells in contact with bone do not exhibit cytoplasmic staining patterns typical of multinucleated osteoclasts. On many occasions, however, mononuclear cells occupy Howship's lacunae which are similar to those lacunae occupied by active multinucleated osteoclasts (Figure 4). The possibility exists that the osteoclast was previously present but moved away, and subsequently the site was occupied by mononuclear cells; these cells could either lie quiescent, remove exposed matrix, as previously mentioned, or actively demineralize the subjacent bone. It is now considered likely that the circulating monocyte may modulate into a macrophage or fibroblast and be capable of contributing an additional nucleus to an existing osteoclast.[17] Recently, however, Mundy[16] has suggested that a single monocyte acting alone can demineralize a bone site directly as well as by producing some dialysable humoral agent not dependent upon preexisting osteoclasts or cells which could also demineralize bone. Similar studies by Teitelbaum[18] imply that the vascular monocyte migrates to the exposed bone site, modulates on bone contact to act as a macrophage, and even coalesces to form a "multinucleated monocyte."

Osteocytic reactions

Osteocytic osteolysis is an enlargement of the lacuna or space normally occupied by an osteocyte. While the size of this lacuna fluctuates slightly during an osteocyte's life cycle, its average size is increased in certain conditions such as hyperparathyroidism and Paget's disease. Also, the size of the lacuna may be larger in fracture callus and woven bone in areas of remodeling near the inflamed joint surface. Periosteocytic demineralization was not seen in sections

which were completely decalcified, as with standard H & E sections. The affected areas were always within 100 microns of inflammatory tissue or marrow changes secondary to the inflammation. While adjacent areas were normal, demineralization was seen in lamellar bone as well as in some areas of woven bone. Such effects could be related to the metabolic processes of the osteocyte itself or to a demineralizing process effected by the bone fluid which passes through the canaliculi in and around the osteocytes buried in the bone (Figure 6). The exposed collagen in these demineralized areas would then become more susceptible to destructive enzymes or other agents derived from the rheumatoid inflammation, thus permitting further damage of these sites and possibly the intrusion of blood vessels into the eroded area. Such deep penetration of bone by superficial enzymes is clearly described by several authors,[19,20] who have shown that peroxidases and lanthanum nitrate are capable of traversing the canaliculi in animal bones to lodge in and around deeply placed osteocytes (Figure 7). Although

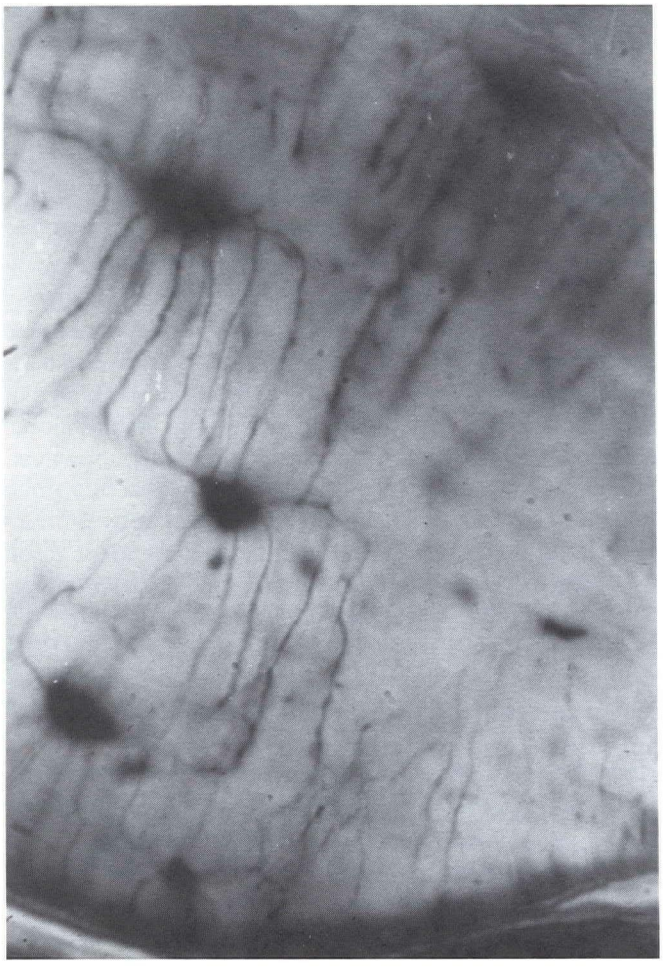

Fig. 6
Osteocytes showing intercommunicating canaliculi (mineralized section, Villanueva Bone Stain x 100).

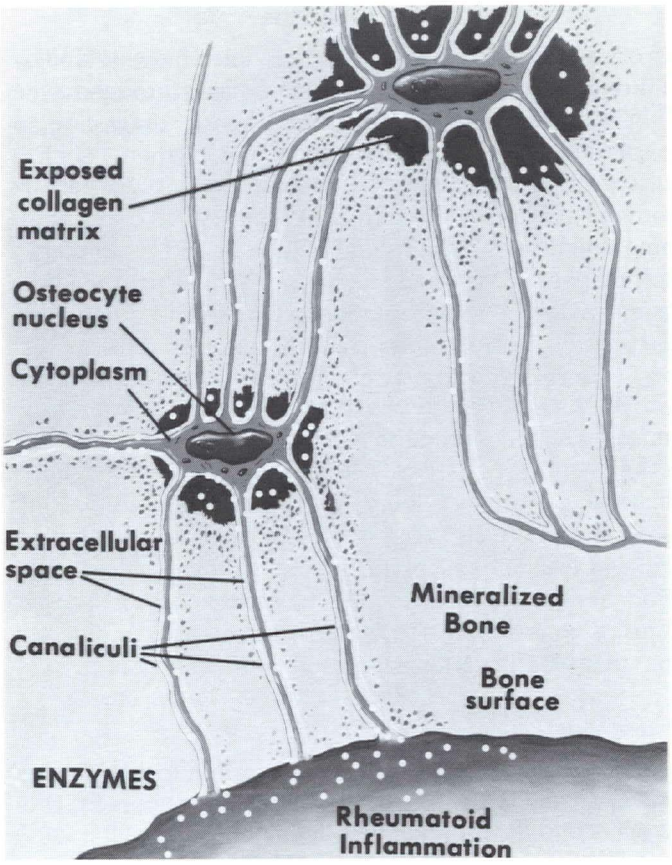

Fig. 7
Schematic representation of passage of extracellular fluid components into domain of deeply placed osteocytes.

this process is not entirely unique to rheumatoid arthritis, it represents a mechanism for the encroachment of the inflammatory tissue deeper into bone.

The types of cellular events in bone erosion are several. The osteoclast remains important, but whether it is exclusively responsible for demineralizing bone is still disputed. The dispute also continues regarding the possibility of an acellular mechanism of demineralization, a freely biochemical / biophysical reaction. There is, however, good evidence to show that biochemical stimulation of the cellular population plays a significant role in destruction of bone in rheumatoid arthritis. From 30 specimens of rheumatoid joints removed for replacement surgery, we have noted not only the dominant effect of multinucleated osteoclasts in the bone damaging process, but also demineralization around some of the buried osteocytes which could be due to the deep penetration of some agents derived from the inflammatory rheumatoid process. Mononuclear cells were seen in areas where bone erosion had occurred, but whether these cells produced a demineralizing effect is still undetermined.

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