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Paget's Disease

Stephen M. Krane, MD*

Ed. Note - This overview was originally presented at the International Symposium on Clinical Disorders of Bone and Mineral Metabolism, May 9-13, 1983. The following list indicates the presentations given in this session at the Symposium and the contents of the corresponding chapter in the Proceedings of the Symposium published by Excerpta Medica. The numbers in parentheses refer to pages in this volume. Complete information about the contents of the Proceedings can be found at the back of this issue.

Paget's disease of bone has been studied extensively by many investigators interested in metabolic bone diseases. Yet Albright and Reifstein (1) pointed out in 1948 that Paget's disease is not generalized and that normal bone can always be identified. The fact that Paget's disease is localized to some but not to all bones was offered as "strong evidence against its being a metabolic or endocrine disorder." Whether or not Paget's disease does belong in the category of metabolic bone diseases, it has been possible to learn a great deal about bone turnover in this disorder and successfully use therapeutic agents to help patients clinically.

We assume that the initial event in Paget's disease is a focal resorption of existing normal bone (2). Histologically, this excessive resorption is shown by the increase in the scalloped resorption spaces (Howship's lacunae) filled with active osteoclasts that are larger and more multinucleated. Even in the earliest biopsies of Pagetic lesions, however, increased osteoblastic activity is evident with the deposition of lamellar or woven bone adjacent to areas of resorption, frequently on opposite surfaces. These events have been interpreted as indicating a marked increase in the "birth rate" of the basic multicellular units of bone (3). Although bone resorption and formation are both increased, the relative increase in resorption is greater than that of normal bone. The uninvolved non-Pagetic bone may not be entirely normal and may show increased resorption and

What is the etiology of Paget's disease and can we cure it? F.R. Singer and B.G. Mills (380)

Do calcitonins help Paget's disease of bone? O.L.M. Bijvoet (389)

Bisphosphonate treatment for Paget's disease of bone. O.L.M. Bijvoet (389)

Mithramycin treatment of Paget's disease of bone exploration of combined therapies—particularly sodium etidronate (EHDP). W.G. Ryan (395)

osteoid surfaces. The latter changes have been interpreted as due to secondary hyperparathyroidism (3).

If resorption is the initial event in Paget's disease and the increases in bone formation are coupled to increases in resorption, then it would follow that if one decreases the resorption rate, the formation rate should also decrease. In fact, it has been possible to decrease bone resorption in Paget's disease by using three different types of agents (calcitonins, diphosphonates, and mithramycin). Indices of bone formation decrease later than those of bone resorption. Although each of these drugs reduces osteoclast function and possibly the generation of new osteoclasts from precursor cells, the activity of the disease eventually returns to pretreatment levels after therapy is discontinued. The Pagetic lesion therefore is not cured. Recent evidence has suggested that Paget's disease is due to infection of osteoclasts or osteoclast precursors by a virus possibly related to measles or respiratory syncytial virus. F.R. Singer and B.G. Mills (pp. 380 ff.) presented the evidence for viral infection of Pagetic cells and discussed the problems in identifying possible agents. If a virus is definitively identified, it will still be essential to prove that

*Department of Medicine, Harvard Medical School and Massachusetts General Hospital, Boston.

Address reprint requests to Dr. Krane, Department of Medicine, Massachusetts General Hospital, 32 Fruit Street, Boston, MA 02114.

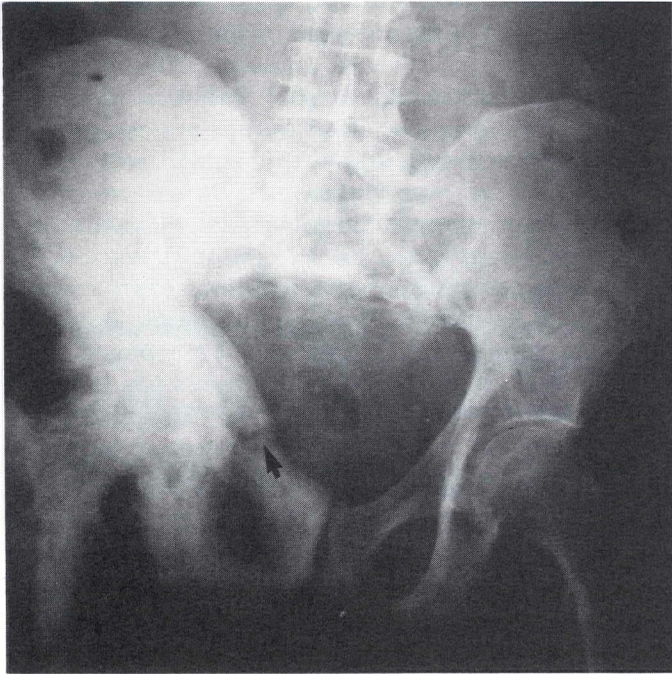


Fig. 1

Radiograph of the pelvis and hips of a patient with Paget's disease of bone. The whole right hemipelvis and proximal femur is involved. The right hip joint has the typical appearance of Pagetic coxopathy with loss of apparent joint space over the entire articular circumference of the femoral head and acetabular protrusion. In addition, there is a pathological fracture (arrow) of the right pubic ramus. These illustrate common complications of Paget's disease.

this agent is the *cause* of the disease and not simply a passenger. If the former is the case, Paget's disease can be cured only if the putative virus is eliminated or if the deleterious consequences of such infection (altered proliferation and function of bone cells) are reversed.

At present, we must treat the clinical problems of Paget's disease (Table). Although most patients are asymptomatic or have relatively little involvement, others must be treated with calcitonin, diphosphonates (bisphosphonates) or mithramycin, or possibly combinations of these drugs. Not all clinical problems are responsive to drug therapy. For example, it is probable that joint disease such as Pagetic coxopathy, once developed, will not be reversed by medical management but will eventually require and respond to total hip replacement. However,

TABLE

Clinical Problems in Patients with Paget's Disease of Bone

1. Pain over lesions
2. Deformities
3. Joint disease
4. Neural compression
5. Propensity to fracture
6. Vascular effects: high bone flow, high cardiac output, "steal" syndromes.
7. Disabling fatigue
8. Hypercalcemia and hypercalciuria
9. Hyperuricemia
10. Tumors: reparative granulomas, malignant neoplasms

other features are responsive, particularly pain over lesions demonstrable radiologically or by bone scan.

Certain aspects of the use of calcitonins were reviewed by Nagant de Deauxchaisnes (pp. 384 ff.). He described the success of calcitonins in improving the focal lesions with apparent healing of the osteolytic disease and replacement with mineralized bone. Bijvoet (pp. 389 ff.) discussed the use of the bisphosphonates and emphasized their extraordinary potency in inhibiting bone resorption. This has been demonstrated in numerous careful studies with etidronate disodium and is reflected in the normalization of the abnormally high urinary hydroxyproline excretion. In Bijvoet's experience, use of etidronate disodium results in clinical improvement in most instances, although some individuals have a temporary increase in bone pain. Fractures were not a problem in his series. Osteolytic Pagetic lesions increased in some individuals, as stressed by Nagant de Deauxchaisnes. In contrast, APD (disodium [3-amino-1 hydroxypropylidene]-1, 1-bisphosphonate), the most potent of the available bisphosphonates appears to arrest osteolytic lesions and helps to fill in defects. Unfortunately, APD has not been approved for use in most countries, including the US. Experience with mithramycin was reviewed by Ryan (pp. 395 ff.). Although this drug effectively reduces abnormal chemical findings in Paget's disease and improves symptoms and abnormal bone scans, it is potentially the most toxic of available drugs and must be used with caution. The long-term remissions that have occasionally been observed after a brief course of therapy have provided impetus for study of further potential uses of mithramycin alone or in combination with other agents.

References

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