Chapter 15. PAGET'S DISEASE OF BONE

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ABSTRACT

Sir James Paget described a skeletal disorder affecting one or more areas of the skeleton in 1876. It is most common in England and in countries to which the English migrated. In recent years the prevalence in most countries has decreased. A common feature is skeletal deformity which evolves over many years and is most visible in the skull and lower extremities. Pathological fractures are most likely to occur in the femurs. Pain is a common feature in patients with Paget's disease and may be of skeletal, joint, neurologic or muscle origin. The radiologic features begin with a localized area of osteolysis which advances very slowly in the absence of therapy. Over time the lesion becomes osteosclerotic and once an entire bone is affected the entire lesion is sclerotic with areas of osteolysis remaining. Bone scans utilizing technetium99m-labeled bisphosphonates exhibit markedly increased uptake in the untreated state. Histologic evaluation of early lesions reveals an increased number of osteoclasts advancing at the interface of normal bone. They are often larger than normal and contain many more nuclei than normal osteoclasts. Subsequently numerous osteoblasts are found to be producing a large amount of disorganized bone. Associated with the increase in osteoclasts and osteoblasts there is a highly vascular fibrocellular marrow replacing the hematopoietic marrow. The osteoclasts have an abnormal ultrastructure featuring nuclear inclusions, and sometimes, cytoplasmic inclusions resembling nucleocapsid-like structures of the Paramyxoviridae family. Measurement of serum or urine N- or C-telopeptides documents the degree of bone resorption and serum total alkaline phosphatase activity, serum bone specific alkaline phosphatase and serum procollagen type 1 amino-propeptide document bone formation. Serum total alkaline phosphatase activity is the least expensive and most widely used test. Patients may develop sarcomas or giant cell tumors in affected bone but this is rare. Metabolic complications include hypercalcemia associated with immobilization and hyperuricemia and gout in patients with more extensive disease. Increased cardiac output may occur in patients with extensive disease due to the vascularity of the lesions. The earliest effective treatment was calcitonin but with the increased efficacy of the more potent bisphosphonates calcitonin is seldom prescribed. The treatment of choice is presently an intravenous infusion of 5 mg zoledronate. This normalizes bone resorption and formation markers for up to six and a half years in most patients. Indications for treatment include bone pain, hypercalcemia, neurologic deficits with vertebral disease, congestive heart failure, preparation for orthopaedic surgery and prevention of complications such as hearing loss and deformity. Surgery most commonly is needed for lower extremity joint replacement and correction of deformities of the lower extremity. The etiology remains somewhat controversial with some studies indicating a role for measles virus. The observation that the prevalence of the disease has decreased could be explained by the introduction of measles vaccine in 1963. Clearly genetic factors also play a role. Mutations in the sequestosome 1 gene produce susceptibility to develop Paget's disease but not all family members with the mutation develop Paget's disease. Other gene abnormalities may also increase disease susceptibility.

HISTORICAL ASPECTS

In 1876, Sir James Paget (Figure 1), a prominent English surgeon, described five men who had at least two deformed areas of the skeleton(1). His description of the disorder he called

osteitis deformans included clinical features, and gross and histologic pathology. He believed he was describing a rare inflammatory disorder, but by the start of the new century, numerous publications describing similar patients appeared in England, France, and the United States. A small number of reports also came from Australia, Germany, Holland, Italy, and Sweden. By this time, the condition commonly became known as Paget's disease of bone.

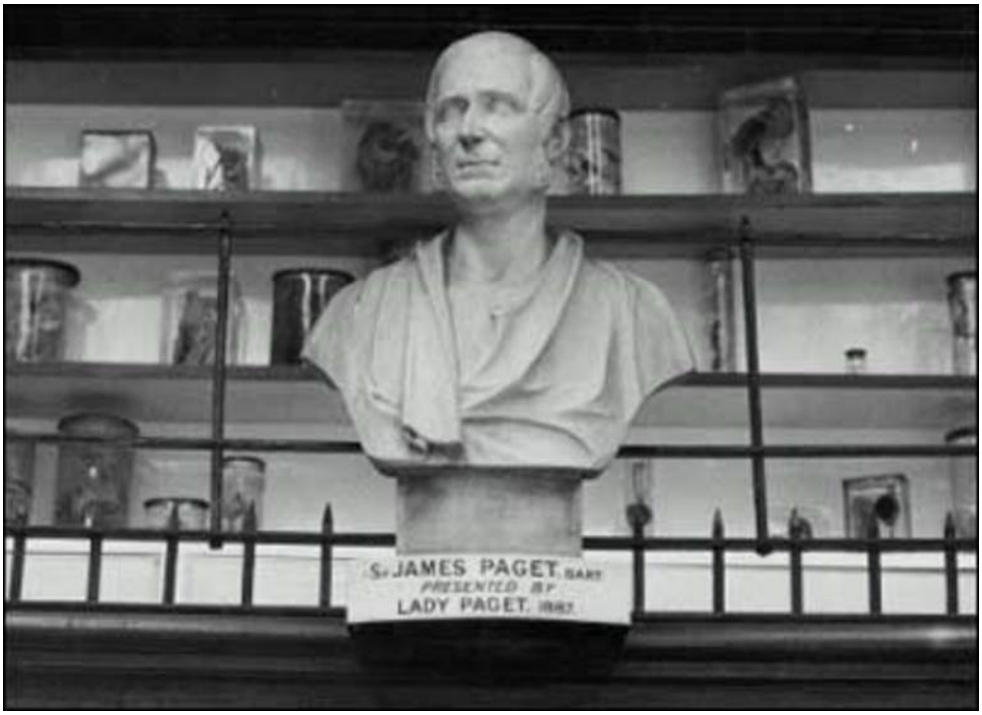

Figure 1. The bust of Sir James Paget in the Museum of St. Bartholomew's Hospital.

Further realization that Paget's disease was not a rare disorder came about after the discovery of X-rays in 1895 by Roentgen. It was then possible to detect affected bones, which exhibited no external manifestations of the disease. The first X-ray report appeared in 1896(2) and osteolytic disease was recognized by 1901(3).

The first biochemical marker of Paget's disease was recognized in 1929 by Kay(4). He reported elevated alkaline phosphatase activity in the patients' sera. Over time, it came to be appreciated that serum alkaline phosphatase activity could reach higher levels in Paget's disease than in any other disorder.

EPIDEMIOLOGY

The distribution of Paget's disease throughout the world is one of its most striking features. While commonly found in the population of England, the United States, Australia, New Zealand, Canada, South Africa, and France, it appears to be rare throughout Asia and Scandinavia. Estimates of the prevalence in individual British cities even suggest a striking variability within one country(5). Analysis of hospital radiographs indicated prevalence ranging from 2.3% in Aberdeen, Scotland to 8% in Lancaster, England. The most recent prevalence estimate in the United States is 1-2%(6), and in France is 1.1-1.8%(7). In many countries the

prevalence of Paget's disease appears to have decreased (8-11) although this has not been observed in Spain (12) or in the Salamanca province of Spain (13). It is particularly difficult to obtain a true estimate of prevalence in a population as serum alkaline phosphatase activity may be elevated in as few as 14% of individuals with x-ray evidence of Paget's disease (14).

Paget's disease probably occurs equally often in men and women and clearly increases in prevalence with age(15). The diagnosis is nearly always determined in individuals over the age of 50 years. The prevalence approaches 10% by 90 years and affected individuals are rarely discovered before 20 years.

The occurrence of Paget's disease in more than one member of a family was first reported in 1883(16). Analysis of numerous kindreds indicates an autosomal dominant mode of inheritance(17). A positive family history of Paget's disease was reported in nearly 15% of patients in two large studies(18,19). In a clinic in Spain, 40% of the patients had at least one first-degree relative with Paget's disease after screening with bone scans(120). Gene analysis of Paget's disease kindreds will be discussed subsequently.

CLINICAL FEATURES

Paget's disease is a localized disorder of the skeleton with a wide range of skeletal involvement. One bone was affected in 5% of patients whereas the average number of lesions was about 6.5 per patient in a series of 197 patients(21). In a more recent study younger patients had a 47% prevalence of monostotic disease while 28% of older patients had monostotic disease(22). In patients with familial disease there may be somewhat more bones affected than in patients with sporadic disease (23).

Deformity

A common feature of Paget's disease is skeletal deformity. This clearly evolves over a period of many years (probably decades) in most patients. The deformity is most visible in the skull and lower extremities.

Asymmetric enlargement of the cranium may first come to attention in those individuals who notice an increase in hat size. An increase in the size of superficial scalp veins, best appreciated over the frontal and temporal bones, is not uncommon. In patients with cranial enlargement, hearing loss is a common complication. The hearing loss correlates with loss of bone mineral density in the cochlear capsule (24). Inexplicably, despite the common skull involvement, Paget's disease is quite unusual in the facial bones. Facial disfigurement may be a consequence of enlargement of the maxilla and/or mandible and can be accompanied by spreading of the teeth, malocclusion, and loss of teeth (25).

One or, less often, two clavicles may become enlarged. An enlarged scapula is uncommonly appreciated perhaps because of its location.

The spine is a common source of morbidity from Paget's disease. The lumbar vertebrae and sacrum are most frequently affected. A single vertebra or multiple vertebrae may be involved. Over time, the vertebrae generally enlarge, but in some instances, vertebral compression may produce significant kyphosis.

Although Paget's disease is commonly found to affect the pelvis, only in its most severe form is it apparent on physical examination that the bone is thicker than normal. It is much easier to detect in the extremities, particularly when bowing of the femur and/or tibia is present (Figure 2). An increase in skin temperature is more readily detected over the tibia, a reflection of increased blood flow to the bone and surrounding soft tissue. Bowing of the upper extremity long bones is much less common than in the lower extremity, presumably because these are not weight-bearing bones.

Figure 2. Typical bowing of the leg due to Paget's disease involving the right tibia.

Pathological fractures in the lower extremity are most likely to occur in the femur and typically are transverse in nature (Figure 3). They are much more likely to result in nonunion than are tibial fractures(26).

Figure 3. Transverse fracture of the left femur.

Pain

Pain is a quite common symptom in the population of Paget's disease patients. It may be of skeletal, joint, neurologic or muscle origin. Surprisingly, bone pain is usually absent even in patients with extensive disease or, when present, is mild to moderate in severity. The pain is usually dull in quality and often persists during the night. Weight bearing seldom produces a significant increase in bone pain.

Severe pain in a patient with Paget's disease is most likely to be due to osteoarthritis. This commonly occurs in the hip joint. Deterioration of the cartilage can occur when Paget's disease affects the acetabulum alone (Figure 4), but is likely to be more severe when both the acetabulum and head of the femur are affected by Paget's disease. If the femoral head is the only site of the disease, osteoarthritis is a less likely complication. A major feature of the pain in these patients is a significant increase in severity with weight bearing. In some patients, the combination of pain and impaired motion of the joint severely limits mobility. Knee pain and joint effusion may be prominent features in patients with bowing of the tibia. Back pain due to osteoarthritis also occurs in association with Paget's disease (Figure 5). Pain from osteoarthritis of the shoulder joint is relatively uncommon.

Figure 4. Paget's disease involving the left hemipelvis and right femur. There is severe osteoarthritis of the left hip but a relatively normal joint space in the right hip.

The most severe chronic pain in patients with Paget's disease is probably of neurologic origin. Pain from compression of the spinal cord or nerve roots may follow from enlargement of the vertebral bodies, pedicles, or laminae as well as from compression fractures. Pain from this source is more likely to arise from Paget's disease affecting the thoracic spine.

Figure 5. Patient with back pain who has multiple vertebrae affected by Paget's disease, large osteophytes, and narrowed disc spaces.

In a number of individuals, the weight of the skull may be so great that they have difficulty in keeping the head erect. This can produce neck pain and tension headaches due to muscle spasm. Deformity of the spine may also be associated with intermittent pain due to spasm of the paravertebral muscles.

RADIOLOGY

The radiologic features of Paget's disease include osteolytic, osteosclerotic, and mixed lesions. The earliest lesions are osteolytic in character and are most readily appreciated in the skull (Figure 6). Circumscribed osteolytic skull lesions were called "osteoporosis circumscripta" by Schuller(27). These most often are seen in the frontal and occipital regions and with time may slowly coalesce. The other region where osteolytic lesions are commonly observed is the long bones of the lower extremity. The lesions usually arise at either end of the bone, seldom in the diaphysis. At the junction of the lesion with normal bone, the osteolytic lesion has the shape of a flame or inverted V (Figure 7). Such lesions have been noted to extend into normal bone at an average rate of about 1 cm per year (28).

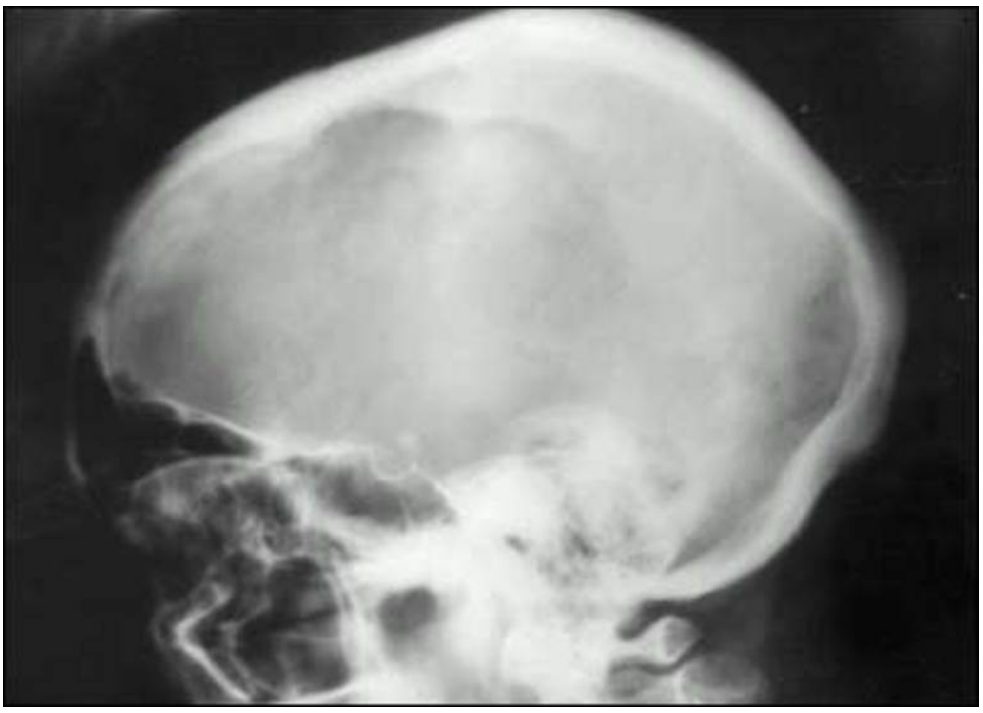

Figure 6. Large osteolytic lesion in the skull of a woman with Paget's disease.

Figure 7. Osteolytic lesion of the distal left femur which is progressing proximally.

A heterogeneous region of osteosclerotic bone slowly develops in areas of the skeleton previously exhibiting a purely osteolytic character. This can be readily seen in long bones where the advancing front of osteolysis is trailed by patchy sclerosis superimposed on the earlier osteolytic process. With more time, the character of the bone may evolve into a dominant osteosclerotic appearance. This is often accompanied by periosteal new bone formation, which results in an increase in circumference of the bone. In the first observations reported by Paget, the thickness of the calvarium was fourfold greater than normal in one patient(1). The most severe skull involvement may be associated with basilar impression (Figure 8) which can produce compression of the structures in the posterior fossa resulting in ataxia, muscle weakness, and respiratory distress. With the evolution of the sclerotic phase of the disease, the lower extremity long bones often exhibit lateral and anterior bowing. Another radiologic feature in the long bones of the lower extremity is the presence of linear transverse radiolucencies in the cortex of the convex aspect of the bowed bone. These have been termed fissure fractures. Multiple fissure fractures may be seen. Although they usually remain stable, a small percent progress to complete transverse fractures.

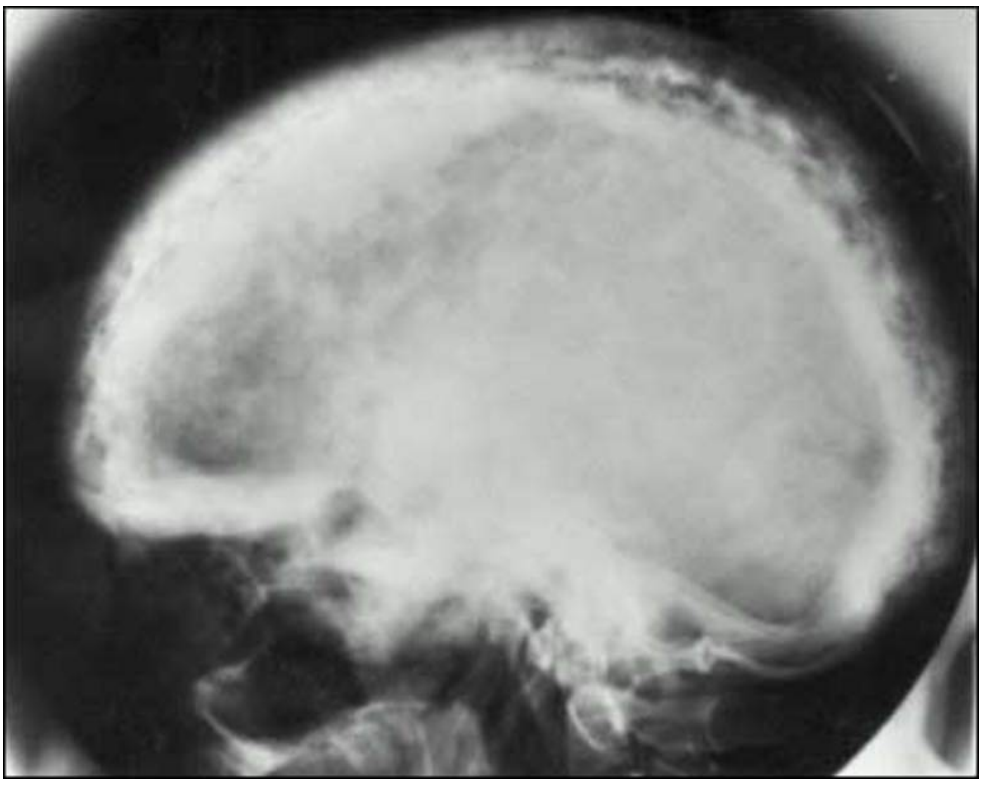

Figure 8. Far advanced Paget's disease of the skull. Note the thickened inner and outer tables, the chaotic new bone deposition termed cotton-wool patch, and basilar impression.

It has been observed that after a dominant sclerotic lesion has developed, there may be secondary osteolytic lesions superimposed upon the sclerotic bone. These are most readily seen as clefts in the cortex of the long bones.

Computerized tomography (CT) and magnetic resonance imaging (MRI) are generally not needed in the evaluation of most patients (29). CT may be needed to detect subtle fractures, spinal stenosis and secondary neoplasms. MRI may be particularly useful in evaluating spinal complications.

The commercial availability of a technetium99m-labeled bisphosphonate in 1974 ushered in the era of routine use of bone scans in clinical medicine(30). In patients with Paget's disease, the affected bone has increased nuclide activity five minutes after intravenous administration of the bone-seeking tracer when compared with normal bone. The nuclide activity is 3-5 times higher than in normal bone. A bone scan is a very effective means of determining the extent of the disease and is clearly more sensitive than X-rays in determining the presence of small osteolytic areas of the disease (Figure 9). Since occult fractures and bone metastases may mimic some lesions of Paget's disease, it is necessary to do X-rays or CT scans of areas of increased nuclide uptake to distinguish the nature of the lesions. Very seldom is it necessary to do a bone biopsy to ascertain the diagnosis.

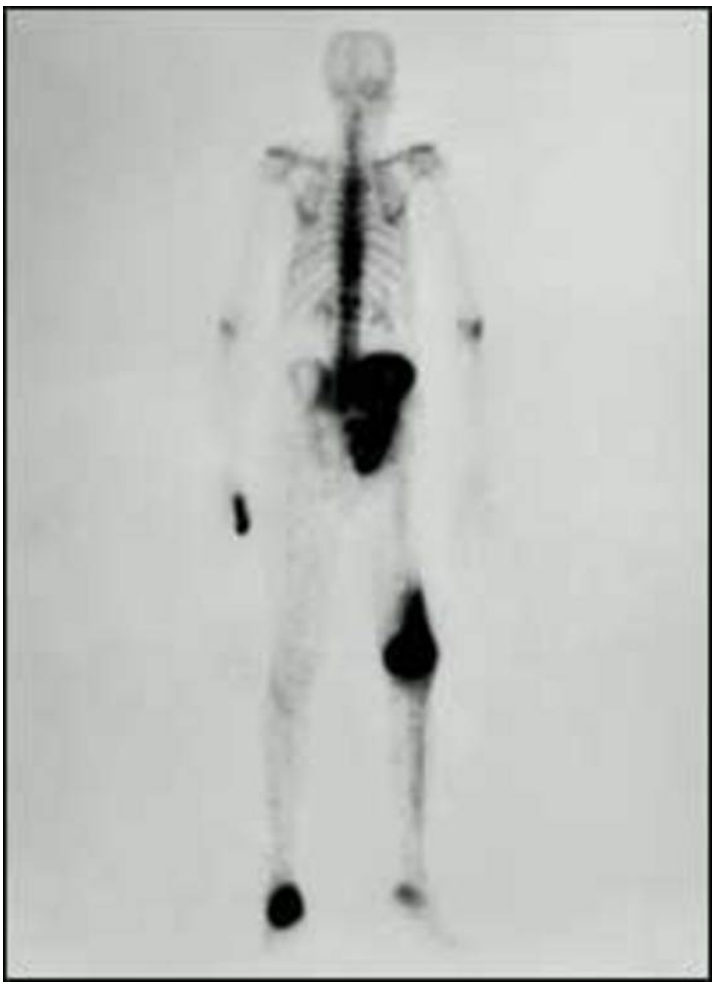

Figure 9. A technetium 99m-bisphosphonate bone scan of a patient with polyostotic Paget's disease.

In addition to the classical bone scan using a technetium-labeled bisphosphonate gallium scans (31), fluorine-18-FDG PET scans(32), and Tl-201 scans(33) have been observed to delineate lesions of Paget's disease. In one study, the response to calcitonin treatment was more rapid with gallium scan than with a bone scan(31).

PATHOLOGY

Based on histological examinations of the interface of normal bone with an advancing osteolytic focus of Paget's disease, it has been concluded that the primary abnormality is a localized excess of osteoclastic bone resorption. An increased number of osteoclasts are present in Howship's lacunae in cortical and trabecular bone(12)(Figure 10). They are frequently larger than normal and may have up to 100 nuclei in a single cross-section rather than the 3-10 found in normal osteoclasts(34). With progression of osteoclastic activity in the cortex, bone volume is reduced and individual osteons become confluent. The bone volume in trabecular bone of the medullary cavities is similarly reduced by osteoclastic activity. In

association with the intense osteoclastic activity, the normal fatty or hematopoietic marrow is replaced by a fibrocellular stroma, which is highly vascular.

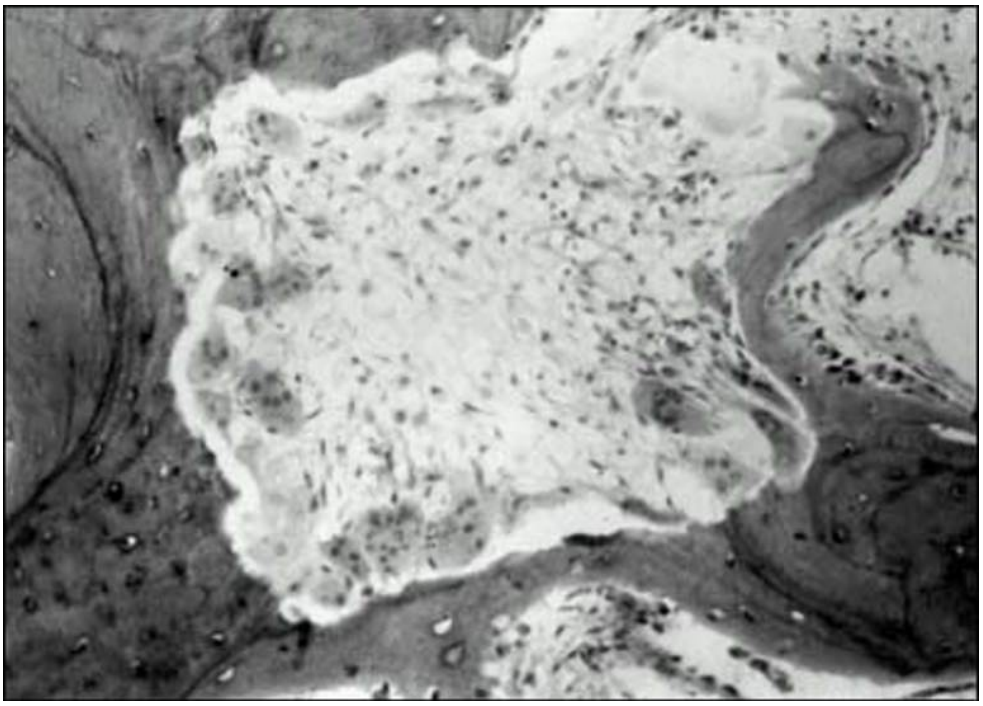

Figure 10. A bone biopsy of the iliac crest revealing an intense area of osteoclastic bone resorption. The osteoclasts are increased in size and have a greater number of nuclei than average.

In the mature lesion, there is a mixture of lamellar and woven bone, which transforms the matrix into a chaotic "mosaic" pattern of irregularly juxtaposed pieces of lamellar bone, interspersed with woven bone(Figure 11). The normal outer and inner circumferential lamellae and interstitial lamellae of the cortex are completely disrupted. Plump osteoblasts are found in large numbers on surfaces of new bone formation. There is an abundance of osteoid on bone surfaces but there is no increase in thickness of the osteoid seams(35).

It has been noted that the size of the periosteocytic lacunae in the woven bone is greater than in the lamellar bone of Paget's disease (35). Since this is also the finding in woven bone from nonpagetic individuals the relevance of this observation is unclear.

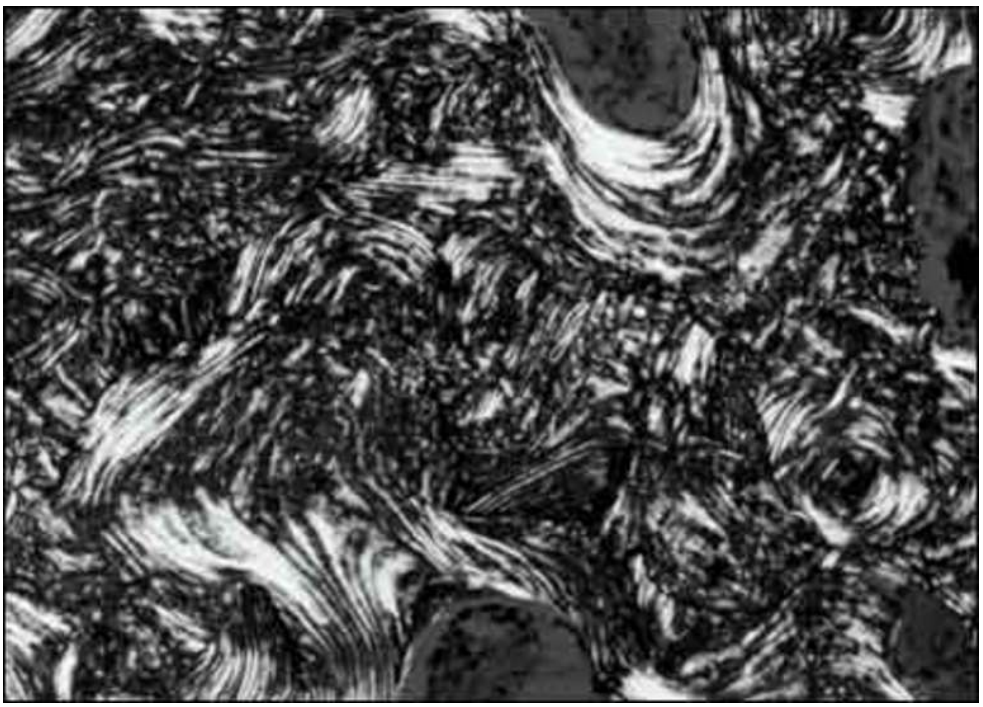

Figure 11. A bone biopsy demonstrating the "mosaic" pattern of bone matrix in Paget's disease. Note the chaotic lamellar pattern intermixed with woven bone as demonstrated with polarized light.

There is some evidence of a "burned out" phase of Paget's disease in which the abnormal matrix persists but cellular activity is nearly absent and the marrow space is mainly filled with fat. It is more likely that such a finding does not occur throughout an entire lesion, but is found with all stages of the disease in a single bone.

Studies of the ultrastructure of osteoclasts in Paget's disease have demonstrated that many of these cells harbor microfilaments in the nucleus and occasionally, in the cytoplasm(36,37) (Figure 12). The microfilaments have the same structural features as nucleocapsids of viruses of the Paramyxoviridae family, a family of RNA viruses known to cause childhood infections such as measles and pneumonia due to respiratory syncytial virus. The nucleocapsid-like structures have not been found in osteoblasts, osteocytes, or bone marrow cells in the same specimens containing the osteoclast microfilaments. Identical microfilaments have been found in a small percentage of the osteoclasts in giant cell tumors of bone and in the osteoclasts of some patients with osteopetrosis and pyknodysostosis(38).

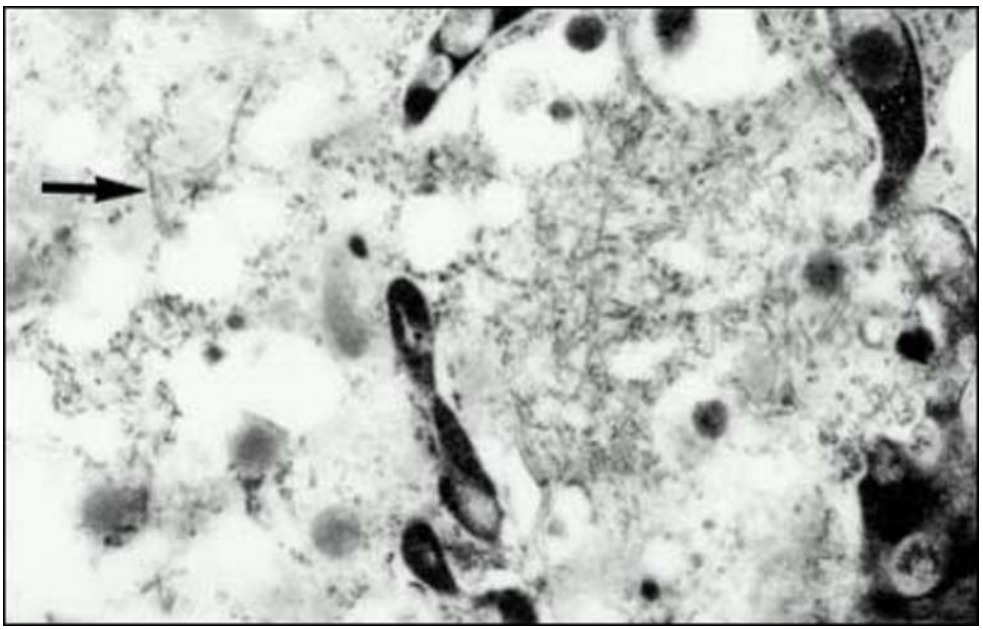

Figure 12. Electron microscopic examination of an iliac crest biopsy revealing microfilaments within remnants of a degenerating osteoclast nucleus. The arrow indicates microfilaments in adjacent cytoplasm. Magn. x 25,800

In addition to the structural evidence for the presence of viral nucleocapsids in the osteoclasts of Paget's disease, evidence of paramyxoviridae nucleocapsid proteins (39,40) and mRNA (41) has been reported, although not by all investigators (42). In one study addressing the identity of the osteoclast microfilaments, the full-length sequence for the measles virus nucleocapsid gene was delineated from the bone marrow of one patient as were more than 700 base pairs of the nucleocapsid gene in three additional patients (43).

BIOCHEMICAL ASSESSMENT

The radiologic and histologic evidence of increased bone resorption and formation in patients with Paget's disease is readily assessed by measuring biochemical markers of bone turnover. In general, these tests reflect the extent and activity of the disease.

Bone Resorption

Since the underlying cellular abnormality in Paget's disease seems to be increased bone resorption, one might expect that serum calcium and/or urinary calcium levels would be increased in some individuals with active Paget's disease. In the absence of fractures, immobilization, primary hyperparathyroidism, or bone metastases, this is not the case (44). Presumably, this is explained by a concomitant increase in bone formation, which has been defined by histopathology and by kinetic analysis of plasma disappearance rates and skeletal uptake of radiocalcium (44). Evidence of increased bone matrix resorption was first provided by the demonstration of increased urinary hydroxyproline excretion, a component of all types of collagen. Subsequently, more specific indices of bone resorption have been developed including pyridinoline, deoxypyridinoline, type I collagen N-telopeptide and C-telopeptide. The

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latter two collagen components are the most specific markers of bone collagen resorption (45); serum and urine assays of the telopeptides are widely available for clinical use.

Bone Formation

Measurement of total serum alkaline phosphatase activity has been a means of evaluating Paget's disease for more than 80 years(4). The enzyme activity, which is localized in the plasma membrane of osteoblasts before extracellular release, correlates with the extent of the disease on skeletal surveys (46) and with parameters of bone resorption (46). The circulating enzyme activity usually increases gradually or does not change during long-term follow up of patients who are untreated (47). In patients with liver disease or who might be pregnant, it would be preferable to measure bone-specific alkaline phosphatase levels by immunoassay (48). Several of these assays have been developed which have little cross-reactivity with nonskeletal alkaline phosphatase. More recently measurement of serum procollagen type1-N-terminal peptide has proven to be valuable in assessing the response to teriparatide in osteoporosis patients. While these assays may have an advantage over the nonspecific total alkaline phosphatase activity with respect to specificity (45), no study has been done which indicates that they should replace this inexpensive assay for routine clinical use (49).

Other markers of bone formation such as serum osteocalcin or type I procollagen carboxyl-terminal peptide are not as sensitive as total or bone-specific alkaline phosphatase levels in assessing the response to therapy (45).

Sclerostin is an important protein produced by osteocytes which inhibits bone formation. Serum sclerostin has recently been noted to be elevated in patients with Paget's disease (50) but is not correlated with serum C-telopeptide or serum procollagen type1-N-terminal peptide levels. The relevance of this finding remains to be established.

Calciotropic Hormones

Serum parathyroid hormone levels are generally normal in patients with Paget's disease(21). Elevated levels are found in the presence of concomitant primary hyperparathyroidism (51) and would be expected to also be increased in the presence of renal failure or vitamin D deficiency. Serum calcitonin levels are normal in Paget's disease (52) although there was prior speculation that low levels might contribute to the pathogenesis of the disease. In the absence of vitamin D deficiency, serum 25-hydroxy-vitamin D and 1, 25 dihydroxyvitamin D levels are normal. Inexplicably, 24,25-dihydroxyvitamin D levels have been reported to be low (53).

NEOPLASTIC COMPLICATIONS

Sarcoma

Sarcomas develop in the lesions of Paget's disease more often than in an age-matched normal population, although the incidence is less than 1% overall (54). However, in patients with extensive disease, the incidence has been estimated at 10% (55), although a subsequent study suggests this is not so (56). Rarely, sarcomas have been known to develop in multiple members of a family.

A sarcoma should be suspected when new pain and swelling develop in a bone previously affected by Paget's disease. The most common sites are in the pelvis, femur, humerus, skull, and facial bones.

There is a variable histology of the sarcomas of Paget's disease including osteosarcoma, fibrosarcoma, chondrosarcoma, and anaplastic sarcoma(55). Several types of histology may be present in a single tumor. Multinucleated giant cells (probably osteoclasts) may be scattered throughout a tumor. They may contain the nuclear microfilaments seen in the osteoclasts and are not thought to be neoplastic in nature (57).

Because of the underlying distortion of the pagetic bone, it is difficult to detect an early stage of a sarcoma. Typically, a radiolucent focus with speckled regions of calcification will be observed to disrupt the cortex of the bone (Figure 13). The best means of delineating the extent of the tumor mass is by CT or MRI.

Figure 13. Multiple sites of osteogenic sarcoma in a patient with Paget's disease of the right hemipelvis. Note the extension of the tumor through the cortex of right ischium.

Perhaps because of a failure of early diagnosis in most patients with sarcoma arising in Paget's disease, survival is brief. Only 7.5%-10% of patients survive five years and despite the multiple modalities of therapy presently available, the prognosis remains poor(55,58).

Giant Cell Tumor

Giant cell tumors of bone may arise in lesions of Paget's disease, often in the skull and facial bones (59). They are nearly always benign and appear to be less common than sarcoma in Paget's disease. As is the case with sarcoma, they rarely may appear in multiple family members who have Paget's disease (60).

A prominent feature of the tumors is the presence of large numbers of multinucleated giant cells, a small percentage of which contain the nuclear microfilaments typical of the osteoclasts

of Paget's disease (59). The neoplastic component of the giant cell tumor is a spindle-shaped cell with fusiform nuclei and clumped chromatin. These cells rarely have mitoses. There may be some difficulty in distinguishing these tumors from giant cell reparative granulomas, which commonly arise in the jaws (61).

Giant cell tumors in Paget's disease are usually successfully treated with surgery and radiation therapy. In a few patients, high doses of dexamethasone have been shown to shrink the tumors (62).

Other Neoplasia

Other neoplastic processes such as lymphoma (54), multiple myeloma (54), various carcinomas, and parathyroid tumors (51) have been reported in association with Paget's disease, but are probably chance occurrences. Metastatic cancers have been reported to metastasize to the highly vascular lesions of Paget's disease.

SYSTEMIC COMPLICATIONS AND ASSOCIATED DISEASES

Hypercalcemia

Hypercalcemia may occur as a consequence of immobilization in patients with Paget's disease (63), although this is an unusual clinical event. This is believed to occur because immobility results in increased bone resorption and decreased bone formation.

Hypercalcemia can also occur in association with a malignancy(64). More commonly hypercalcemia in Paget's disease occurs as a consequence of primary hyperparathyroidism (51). Correction of the hyperparathyroidism by surgery produced a decrease of 68% in plasma alkaline phosphatase in a series of 18 patients (51). The clinical features of these patients were quite similar to hyperparathyroid patients without Paget's disease, prompting the investigators to speculate that the two diseases were associated by chance.

Hyperuricemia and Gout

Hyperuricemia has been observed to be common in males with relatively severe Paget's disease (46). Clinical episodes of gouty arthritis occurred in almost half of these individuals. In a larger population of Paget's disease patients, hyperuricemia (20%) and gout (4%) were not felt to be increased in incidence (65). The differences in hyperuricemia and gout might be explained by the severity of the disease in the two study populations. With extensive skeletal involvement, a high turnover of nucleic acids in the lesions of Paget's disease could increase the urate pool enough to produce a clinical disturbance of urate metabolism (66).

Cardiovascular Dysfunction

A hallmark of the pathology of Paget's disease is the increased vascularity of affected bones. Further evidence for this has been documented by demonstration of an increase in blood flow to the extremities (67), although it has been suggested that this is mainly caused by cutaneous vasodilation (68). An echocardiographic study of cardiac function in Paget's disease found that patients with more severe disease had lower peripheral vascular resistance and higher stroke

volume (69). These observations help account for the finding that patients with 15% or more of their skeleton affected by Paget's disease have increased cardiac output (70).

It is possible that increased cardiac output in patients with Paget's disease accounts for an increased incidence in calcific aortic stenosis through causing turbulence across the valve. Patients with Paget's disease have a 4-6 times higher incidence of this lesion than control subjects (71,72). Calcification of the interventricular septum has also been reported in patients with Paget's disease and may be associated with complete heart block (72,73). It also has been reported that arterial calcification is more common in Paget's disease than in control subjects in the aorta as well as in iliac, femoral, gluteal and pelvic arteries (74). The explanation for this is unknown.

A less certain consequence of an increase in vascularity of bone and surrounding soft tissues is a variety of vascular steal syndromes. Patients with marked enlargement of the skull have been noted to be withdrawn, somnolent, and weak. These findings might be explained by shunting of blood from brain vessels to the external carotid artery system (75). It has also been proposed that spinal cord dysfunction might be a consequence of shunting of blood flow from the spinal arteries to the bone (76).

DRUG THERAPY

Prior to 1975, a number of nonspecific treatments were used to attempt to alleviate some of the manifestations of Paget's disease. With the exception of pain medications none were of value. With the development of salmon calcitonin a new era of effective treatment began. Presently, there are a number of highly effective agents which make possible excellent control of the disease.

Pretreatment Evaluation

The initial goal of patient evaluation is to establish which bones are affected by Paget's disease and what symptoms the lesions produce. A search for skeletal deformity may indicate one or more bones are involved, but this should be confirmed by X-rays. The full extent of the disease would best be ascertained by full body bone scan followed by radiologic confirmation of the disease in areas of increased tracer uptake. The decision as to which patient requires a bone scan is an individual one. For example, a 90 year asymptomatic patient who is found to have Paget's disease in the pelvis during an intravenous pyelogram probably does not need a scan.

There is now a considerable choice of bone resorption and bone formation parameters which could be used to determine the overall metabolic activity of the disease. For routine clinical purposes, in most patients, measurement of total serum alkaline phosphatase activity is an effective and inexpensive test.

Calcitonin

Calcitonin is a peptide hormone whose main pharmacologic effect is rapid inhibition of bone resorption. This is mediated by binding of the hormone to its receptor on the surface of osteoclasts.

Salmon calcitonin was the first calcitonin species approved by regulatory agencies for treatment of Paget's disease. A dose of 50 to 100 U given daily or three times a week produces relief of bone pain in most patients within 2-6 weeks. Following suppression of the metabolic activity of the disease cardiac output is reduced (77) as is the skin temperature over affected tibiae. In addition, some patients have had dramatic improvement of neurologic deficits (78). Stabilization of hearing loss has also been noted (79). Because the drug has been shown to reduce the vascularity of bone affected by Paget's disease, it has been given preoperatively to reduce the degree of hemorrhage in patients scheduled for orthopaedic procedures (80).

A single injection results in an immediate decrease in urinary hydroxyproline reflecting an acute inhibition of bone resorption. A maximal effect occurs in several months. Serum alkaline phosphatase activity falls more slowly; a significant decrease is generally not seen for one month. Within 3-6 months, both hydroxyproline excretion and alkaline phosphatase activity decrease on average by 50%. If treatment is stopped, urinary hydroxyproline gradually increases over several months followed by an increase in alkaline phosphatase activity back to pretreatment levels. With chronic treatment osteolytic lesions generally are reversed (81). However, if treatment is not continuous, the osteolytic lesion will recur. Reduced uptake of radiolabeled bisphosphonate (82) and gallium (31) occurs during long term treatment. Bone biopsies exhibit a reduced number of bone cells, a decrease in marrow fibrosis, and a reduction of woven bone volume (83).

Since salmon calcitonin is a foreign protein, it is not surprising that more than half of patients on long-term treatment develop specific antibodies against the hormone in the circulation (84). High titers of these antibodies almost always impair the response to continuing treatment so that up to 26% of patients have become resistant to the drug. Although no longer available for clinical use, human calcitonin was effective in inducing remissions in salmon calcitonin-resistant patients. Presently, any of the bisphosphonates can be used to treat these patients.

Salmon calcitonin injections may cause nausea and facial flushing in 10-20% of patients. Vomiting, abdominal pain, diarrhea, and polyuria are much less common side effects. Rarely tetany and allergic reactions have been reported. Nasal spray salmon calcitonin is much less likely to cause side effects but has lower potency (85). At this time, salmon calcitonin is used much less frequently than in the past because of the development of potent bisphosphonates.

Bisphosphonates

The development of the bisphosphonates for the treatment of skeletal disorders associated with increased bone resorption has been a major advance in the management of Paget's disease (86). These drugs, initially known as diphosphonates, are analogues of inorganic pyrophosphonate, a factor believed to be a necessary component for the mineralization of bone. All bisphosphonates have a central P-C-P core, which was substituted for the naturally occurring P-O-P core of pyrophosphate, because unlike P-O-P, the P-C-P structure is impervious to metabolic degradation. The bisphosphonates have a profound influence on bone metabolism, in part, because they bind to hydroxyapatite. The primary effect of bisphosphonates is to inhibit osteoclastic bone resorption, which in vivo is followed by a secondary decrease in bone formation. The earliest bisphosphonates which were developed, etidronate and clodronate, appear to achieve their effects by generating nonhydrolyzable analogues of adenosine triphosphate, while the later generation of more potent aminobisphosphonates, such as pamidronate and risedronate, inhibit protein prenylation through inhibition of farnesyl pyrophosphate synthase, a key enzyme in the mevalonate

pathway. Although it is generally believed that bisphosphonates act directly on the differentiation and function of osteoclasts, evidence has accumulated which indicates that some bisphosphonates regulate cell proliferation, differentiation and gene expression in human osteoblasts in vitro (87). How such observations translate into in vivo actions of bisphosphonates is unclear.

In table I, the bisphosphonates presently approved for treatment of Paget's disease in the United States are listed with their recommended regimes. There are four oral bisphosphonates available whose recommended daily treatment courses range from two months to six months and two intravenous bisphosphonates.

Table 1.

Bisphosphonates available in U.S.A.	**Administration and Dosage**
Etidronate Trade Name: Didronel® FDA approval: 1977	**1. Tablet** **2. 200 to 400 mg once daily for 6 months** **3. 200-400 mg dose is approved; 400 mg dose is preferred** **4. Must be taken with 6-8 ounces of water on an empty stomach (no food, beverages, or medications for 2 hours before and after dose).** **5. Course of Didronel® should not exceed 6 months.** **6. Repeat courses can be given after rest periods of 3-6 months duration.**
Pamidronate Trade Name:Aredia® FDA approval: 1994 Generic available	**1. Intravenous** **2. Approved regimen is 30 mg intravenous infusion over 4 hours on 3 consecutive days** **3. A more commonly used regimen is a 60 mg or 90 mg intravenous infusion over 2-4 hours and repeated as clinically indicated.** **4. A single infusion is sometimes effective in mild disease; 2-3 or more infusions may be required in more severe disease.** **5. A course of Aredia® may be readministered at intervals as needed.**
Alendronate	**1. Tablet** **2. 40 mg once daily for 6 months· Must**

Bisphosphonates available in U.S.A.	Administration and Dosage
Trade Name:Fosamax® FDA approval: 1995 Generic available	**be taken on an empty stomach, with 6-8 ounces of water, in the morning.** **3. Wait at least 30 minutes after taking Fosamax® before eating any food, drinking anything other than tap water, or taking any medication.** **4. Do not lie down for at least 30 minutes after taking Fosamax®. (Patient may sit.)** **5. Available by mail order to the general public.**
Tiludronate Trade Name:Skelid® FDA approval: 1997	**1. Tablet** **2. 400 mg (two 200 mg tablets) once daily for 3 months** **3. Must be taken on an empty stomach with 6-8 ounces of water.** **4. Skelid® may be taken any time of day, as long as there is a period of 2 hours before and after resuming food, beverages, and medications.**
Risedronate Trade Name:Actonel® FDA approval: 1998	**1. Tablet** **2. 30 mg once daily for 2 months** **3. Must be taken on an empty stomach, with 6-8 ounces of water in the morning.** **4. Wait at least 30 minutes after taking Actonel® before eating any food, drinking anything other than tap water, or taking any medication.** **5. Do not lie down for at least 30 minutes after taking Actonel®. (Patient may sit.)**
Zoledronic Acid Trade Name: Reclast®	**1. Intravenous** **2. A 15 minute infusion of 5mg** **3. Creatinine clearance must be ³35 ml/min** **4. Correct vitamin D deficiency and/or**

Bisphosphonates available in U.S.A.	Administration and Dosage
FDA approval: 2007	**hypocalcemia before infusion** **5. To reduce the risk of hypocalcemia after infusion, patients should receive 1500mg calcium and 1000 units vitamin D3 daily for two weeks**
*Adapted from Information for Patients about Bisphosphonates, A Publication of the Paget Foundation for Paget's Disease of Bone and Related Disorders (2007).	

The least potent bisphosphonate, etidronate, is similar to salmon calcitonin with respect to suppression of the metabolic activity of Paget's disease. The more potent aminobisphosphonates, pamidronate, alendronate, risedronate, and zoledronic acid can induce biochemical remissions in the majority of patients. In the past patients with extensive disease and markedly elevated biochemical parameters may have impressive reductions in serum alkaline phosphatase activity yet not reach normal levels (88). However, patients treated with zoledronic acid, no matter how high the baseline serum alkaline phosphatase activity, nearly always reach the normal range of enzyme activity (89). Most of the clinical benefits attributed to salmon calcitonin are produced by the aminobisphosphonates, yet it remains to be demonstrated whether long term biochemical remissions with any agent can reduce the incidence of future complications such as hearing loss and deformity.

The oral bisphosphonates are poorly absorbed and must be taken with water only. In clinical trials, side effects involving the gastrointestinal tract were not greater in patients receiving the drug than in the placebo group. However, some individuals experience abdominal distress or diarrhea. Patients receiving an oral aminobisphosphonate are advised to remain upright for at least 30 minutes after taking the drug to reduce the chance of esophageal irritation. A small percentage of patients may experience a transient increase in bone pain. The first infusion of pamidronate (90) or zoledronic acid (89) may produce an acute phase reaction in 30-50% of patients manifested by fever, myalgia, and elevation of circulating interleukin 6 levels (90). Subsequent infusions produce little or no side effects. The mechanism responsible for the acute phase reaction appears to be release of cytokines from gamma delta T cells (91) which is worsened by vitamin D deficiency (92). Allergic reactions to bisphosphonates are rare and most commonly manifest as inflammatory eye reactions due to pamidronate (93). If etidronate is used at a dose greater than 5 mg/kg body weight, osteomalacia may be a consequence (94). Another disadvantage of etidronate use is that osteolytic lesions may progress despite evidence of biochemical improvement (81).

Treatment with a potent bisphosphonate may produce long remissions. This is the most likely to be seen after treatment with zoledronic acid. A single infusion restores biochemical markers of bone turnover into the normal range and this is maintained for up to six and a half years in most patients (95). This response is largely independent of pretreatment disease activity. However, with the older bisphosphonates induction of a remission correlates well with the extent and activity (alkaline phosphatase) of the disease (96). Patients with less extensive disease and lower alkaline phosphatase activity are more likely to achieve remission. With respect to the duration of a remission, this appears to be dose-dependent as well as correlated with the nadir value of serum alkaline phosphatase activity, the number of affected bones and the number of previous therapies (96).

Resistance to etidronate therapy is commonly seen after two six month courses of the drug (97). There is also evidence that resistance to intravenous pamidronate (96) or clodronate (97) can occur. In pamidronate-resistant patients, treatment with alendronate was effective (98). In the clodronate-resistant patients, either risedronate or pamidronate was effective (99). There is no information which explains the mechanism responsible for apparent decreased efficacy of these agents with time. It is possible that an increase in the disease activity is responsible for these observations rather than a change in efficacy of the drugs.

Considerable publicity has been given to the development of osteonecrosis of the jaw in patients treated with bisphosphonates (100). This mainly is seen in cancer patients given monthly infusions and is rare in patients with Paget's disease.

Miscellaneous Agents

Other inhibitors of bone resorption such as plicamycin and gallium nitrate, approved for treatment of hypercalcemia of malignancy, are effective in treating Paget's disease (101,102). In view of the safety and efficacy of the aminobisphosphonates, there is very little present use of these agents. The most potent antiresorptive agent, denosumab, has been reported to decrease disease activity in one patient with Paget's disease (103).

Treatment and Posttreatment Evaluation

Assessment of total serum alkaline phosphatase activity is generally sufficient to determine the success of treatment. The frequency of evaluation does not need to be more frequently than every 3 months after the onset of the treatment and can be extended to every 6-12 months after a nadir has been reached.

If a patient has a well defined osteolytic lesion on X-ray, it can be assessed annually to assure the disease is well-controlled. Serial nuclear scans of the skeleton are not necessary.

Indications for Treatment

Effective drug treatment for Paget's disease has evolved over 40 years, but there have been no large, randomized, long-term clinical trials, which can provide definitive guidelines for treatment. Nevertheless, in table 2, indications for drug treatment of Paget's disease are listed. These are based on a review of the literature and a large personal experience.

Table 2.

Indications for Drug Treatment of Paget's Disease
1. Bone pain
2. Hypercalcemia due to immobilization
3. Neurologic deficit associated with vertebral disease
4. High-output congestive heart failure
5. Preparation for orthopaedic surgery
6. Prevention of complications including hearing loss, deformity

Although bone pain is not a problem in the majority of patients, it is a clear indication for treatment. In patients in whom bone pain is difficult to distinguish from joint pain treatment of the Paget's disease will usually clarify the source of pain. Treatment should also correct hypercalcemia in an immobilized patient, a rare situation. Neurologic deficits may improve with treatment, also a very unusual complication. High output heart failure should respond favorably to a treatment which lowers the cardiac workload. Reducing the vascularity of the bone and surrounding soft tissue before elective orthopaedic surgery should reduce perioperative bleeding.

A major indication for treatment could be the prevention of future complications. There is some evidence that progression of hearing loss is reduced by treating patients with cranial disease. Prevention of deformity of lower extremity long bones and secondary osteoarthritis is a reasonable possibility. Presumably, early treatment would reduce the incidence of future fractures. It would be more speculative as to whether the incidence of sarcoma or giant cell tumor formation would be influenced.

To achieve the long term goals of therapy such as prevention of future complications, it may be necessary to maintain the serum alkaline phosphatase activity within the normal range. Future very long term studies would be needed to determine if complications can be abolished.

Surgery

In table 3, the various surgical procedures which have been utilized in the management of Paget's disease are listed.

Table 3.

Surgical Procedures for Management of Paget's Disease
1. Total hip replacement
2. Total knee replacement
3. Femoral osteotomy
4. Tibial osteotomy
5. Suboccipital craniectomy and upper cervical vertebral laminectomyfor basilar impression
6. Ventricular shunting for hydrocephalus
7. Stapes mobilization or stapedectomy
8. Surgery for correction of spinal stenosis or nerve root compression

Total hip replacement is probably the most common elective orthopaedic procedure in patients with Paget's disease (104, 105)). Pain relief and improved mobility occur in a high percentage of patients. Postoperatively, heterotopic ossification may be somewhat more common, but is seldom a significant problem. For patients with severe osteoarthritis of the knees, total knee

replacement is an effective treatment (106). Knee pain and joint effusions associated with osteoarthritis and tibial bowing can be effectively treated by tibular and fibular osteotomy (80).

There is much less experience with neurosurgical procedures in treating Paget's disease. However, successful relief of symptoms is expected after surgery for spinal stenosis or nerve root compression (107). Percutaneous vertebroplasty might be considered in patients thought to have vertebral bone pain who do not respond to conservative therapy (108).

Stapes mobilization or stapedectomy has not proven to be effective in improving hearing loss. One patient treated with cochlear implantation was reported to have improved speech perception (109).

ETIOLOGY

Slow Virus Infection

The possibility that Paget's disease fell into the category of a slow virus infection was suggested by the observation that the osteoclasts in this disorder harbored nuclear and cytoplasmic microfilaments which were essentially identical in structure to nucleocapsids of the Paramyxoviridae virus family(33,34). Immunochemical studies (36,37), molecular studies(38), and sequence analysis of nucleocapsid transcripts(40) have supported the initial hypothesis although not all studies have been positive with respect to a viral presence in the osteoclasts (39). Indirect support for the role of measles virus comes from a consideration of the availability of measles vaccine throughout the world (110). The vaccine was introduced in the United States in 1963, in Australia in 1967, in the United Kingdom and France in 1968, in New Zealand in 1969, in the Netherlands and Italy in 1976 and in Spain in 1978. Availability of the vaccine for about 50 years in several countries might explain a decrease in prevalence whereas delayed availability might explain why other regions may not have had a decrease as yet.

Genetics

Since there is clearly a familial aggregation of Paget's disease in up to 40% of patients with Paget's disease(15,17), a search for a predisposition gene or genes has been undertaken by a number of investigators.

The initial attempts to define genetic susceptibility in Paget's disease centered on chromosome 6 because of known associations between disease susceptibility and histocompatibility loci on this chromosome (111). Although there is some evidence for human leucocyte antigen linkage in families with Paget's disease no gene locus has yet been defined on chromosome 6.

The initial localization of a predisposition gene for Paget's disease came from linkage studies with chromosome 18 markers (112, 113). Attention was given to chromosome 18 because of the discovery that mutations of receptor activator of nuclear factor kB (RANK), a critical osteoclastogenic factor, were responsible for the skeletal disorder, familial expansile osteolysis(114), a condition which bears some resemblance to Paget's disease(115).

Although chromosome markers have indicated linkage to Paget's disease in the region of the RANK gene on chromosome 18, no RANK mutations have been found in families of typical Paget's disease. A second susceptibility locus, not associated with RANK, has been identified on chromosome 18 in a large Australian kindred (116). A further finding of interest on chromosome 18 is that sarcomas arising in Paget's disease may harbor a tumor suppressor gene in the same region as the first locus to be described (117).

In 2002 Laurin and colleagues (118) reported that mutations in the sequestosome 1 gene on chromosome 5 were associated with Paget's disease in 11/24 French Canadian families and in 18/112 apparently sporadic patients. Mutations of this gene were subsequently found in families in the United Kingdom, Australia, New Zealand, the United States and The Netherlands. Mutations have also been found in a small percentage of patients with sporadic disease but the relevance of this finding is unclear. More than 20 different mutations have been described, nearly all of which are clustered around the ubiquitin binding domain of the sequestosome 1 protein (119-121). This protein modulates activity of the NF-κβ pathway, an important mediator of osteoclast function, and has also been implicated in the process of autophagy in osteoclasts (122).

A second gene abnormality has been described in the rare syndrome of inclusion body myopathy, frontotemporal dementia and Paget's disease (123). Nine missense mutations of the gene encoding valosin-containing protein (VCP) had been identified in 20 families by 2007 (124). Only about 50% of the individuals with a mutation have demonstrable Paget's disease (125). VCP has an ubiquitin-binding domain as does sequestosome 1 and like sequestosome 1 is thought to play a role in autophagy (126) A search for VCP mutations in familial and sporadic Paget's disease patients was negative in one study (127) and revealed a polymorphism associated with sporadic Paget's disease in another study (128).

Further evidence of the heterogeneity of the genetics of Paget's disease has come from studies reporting linkage of the disease with candidate loci at chromosome 5q31 and 5q35-qter (129), chromosome 2q36 (130), and chromosome 10p13 (130,131).

In a relatively small group of Paget's disease patients, no mutations of the osteoprotegerin gene were found and a statistically significant increased frequency for the C allele in exon 2 was noted compared to control subjects (132). In a larger study a common polymorphism of the osteoprotegerin gene, G1181C, was found to predispose to the development of sporadic and familial Paget's disease (133). Estrogen receptor-a and calcium-sensing receptor genotyping were significantly different in Paget's disease versus control subjects in another study (134).

In the past five years ten new susceptibility loci for Paget's disease have been reported (135-140). Most of these are likely to influence bone metabolism (CSF1, TNFRSF11A, PML, TM7SF4, UCMA/GRP, DKK1, CTHRC1, OPTN). In one study single nucleotide polymorphisms were believed to amplify the effect of sequestosome 1 mutations and thereby magnify the severity of Paget's disease (141).

Animal Models of Paget's Disease

Transgenic mice have been utilized to investigate the potential roles of the measles nucleocapsid gene and the sequestosome1/p62 and VCP/p97 gene mutations in the pathogenesis of Paget's disease.. Targeting of the measles virus nucleocapsid gene into osteoclasts of transgenic mice produced lesions in some vertebrae which strongly resembled the lesions of Paget's disease, increased osteoclastic activity with exuberant new bone formation often of woven character was observed (142). The same investigators targeted the most common sequestosome1/p62 mutation in familial Paget's disease, P392L, into the osteoclasts of transgenic mice (143). They observed increased numbers of osteoclasts associated with bone loss but no increase in osteoblastic activity characteristic of Paget's disease. Transduced osteoclast precursors isolated from the mice were hyperresponsive to receptor activator of NF-kappa B ligand (RANKL) and TNF-alpha but did not exhibit increased 1,25 (OH)2D3 responsivity, TAF(11)-17 expression or increased number of nuclei per osteoclast, features found in osteoclast precursors isolated from individuals with Paget's disease. In contrast to this study Daroszewska and colleagues did find that targeting the P392L mutation into transgenic mice produced a Paget-like bone pathology predominantly in the lower limbs (144). They also found that osteoclast precursors had increased sensitivity to RANKL in vitro but did not examine 1,25(OH)2D3 sensitivity or TAF(11)-17 expression. They found nuclear inclusions also but it was not certain that they were identical to those found in patients. The explanation for the different results in these two studies is not apparent.

To examine the potential interaction of the measles virus nucleocapsid gene and the P392L mutation Kurihara and colleagues undertook studies of bone marrow specimens from patients with familial Paget's disease who had the P392L mutation, utilizing specimens from pagetic and normal bone as well as from normal volunteers (145). The effects of antisense-measles virus nucleocapsid protein (MVNP) on osteoclast characteristics were different in marrow specimens from pagetic bone versus nonpagetic bone. The patient specimens which had MVNP expression responded to the antisense –MVNP with a reduction in osteoclast number, TATA box-binding protein associated factor 12 expression, 1,25 (OH)2D3 –stimulated IL-6 production and bone resorption, observations indicating a reversal of the usual features of osteoclasts generated from the marrow of sporadic or familial Paget's disease patients. The results indicate an important role of measles virus in pagetic lesions. A contribution of the P392L mutation to the pathologic process was suggested by the fact that there was hyperresponsiveness to RANKL in both the pagetic and nonpagetic bone marrows obtained from the familial patients. These investigators then went on to carry out experiments in transgenic mice by cross breeding mice with MVNP and P392L mutations (145). The mice who harbored both MVNP and P392L had more severe Paget-like lesions than mice with MVNP alone.

Two groups have generated transgenic mice expressing mutant forms of the VCP/p97 gene (146,147). In both studies increased osteoclastic activity appeared to be the dominant histologic feature with a modest amount of sclerotic bone being present. No studies evaluating the characteristics of the osteoclast precursors were reported.

In a recent mouse study it was discovered that osteoclasts obtained from optineurin mutant mice have an increase in NF-kB activation and a reduction in response to RANKL as compared to wild-type mice (148). Bone histology revealed increased osteoclastic activity and increased bone formation but the overall histology was not typical of Paget's disease.

Preliminary studies in mice have led to a proposed model for the coupling of bone resorption to bone formation in Paget's disease (149). MVNP expression in pagetic osteoclasts produces high levels of interleukin-6 which induce ephrin-B_2 on osteoclasts and ephrin-B_4 on osteoblasts

to increase coupled bone formation. MVNP also induces IGF1 expression by osteoclasts which further stimulates bone formation and increases ephrin-B_2.

Clearly great progress has been made in studies of the genetics of Paget's disease but the question remains whether various mutations are a cause of the disorder or whether an individual with a mutation has an increased susceptibility to develop Paget's disease. Results of two clinical studies seem to favor the latter possibility. In a study of 84 offspring from 10 families whose Paget's disease was associated with sequestosome 1 mutations, only 17% of the 23 offspring (mean age 45 years) who had mutations had evidence of the disease as indicated by bone scans(150). The offspring with normal scans had a mean age of 44 years and the mean age of the parents at the time of diagnosis was 48 years. There is incomplete penetrance of the Paget's disease trait in these families although it is possible more offspring will develop Paget's disease in the future. In the other study only 52% of patients with a VCP/p97 gene mutation were noted to have a lesion of Paget's disease after extensive radiologic surveys (125). No assessment of viruses in the bone of these patients has been reported.

Future studies may define other genetic mutations influencing the development of Paget's disease and further understanding the interaction between genetic factors and environmental factors such as the paramyxoviruses..

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