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Paget's Disease of Bone

Medical Grand Rounds

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Case Reports

Case 1 - C.B. is a 74 year old white man referred to the Endocrine Clinic because of hip pain and blastic lesions seen on pelvic films. At the time of presentation the patient also related symptoms of prostatic obstruction. The initial impression was that the blastic changes represented prostatic carcinoma metastatic to bone. Urologic consultation was obtained as were the following laboratory, X-ray, or biopsy results.

acid phosphatase - 0.34 calcium - 10.2
alkaline phosphatase - 112 phosphate - 3.5
bone scan - increased uptake in pelvis and right hip
prostate biopsy - negative for carcinoma

Careful review of the films and comparison to old films revealed no progression in the blastic lesions from three years previously and discovered asceptic necrosis of the right hip that had not been appreciated by his physicians. No treatment was initiated for his old and largely inactive Paget's disease.

Case 2 - H.B. is a 68 year old white man referred to the Endocrine Clinic because of pain and deformity of the left tibia. The patient related a many year history of pain and progressive bowing of the left leg. The patient also stated that his deformed leg was often warmer than his other leg. He had been told that he had Paget's disease in that leg and had been treated with a brace. Initial evaluation included the following laboratory and X-ray results.

alkaline phosphatase - 228 calcium - 9.7
phosphate - 3.5
bone scan - increased uptake restricted to the left tibia
X-ray - bowed left tibia with typical blastic changes of Paget's disease

The patient was placed on therapy with sodium etidronate. With this treatment local heat disappeared, pain markedly decreased, and the alkaline phosphatase value decreased to 110.

Case 3 - S.S. is a 53 year old white man sent to the Endocrine Clinic for treatment of extensive Paget's disease. The patient had initially been diagnosed at the Houston VAMC after radiographs of his foot demonstrated changes consistent with the diagnosis of Paget's disease. Prior to coming to this medical center he had received no specific treatment for his disease and had complaints relating to his back, pelvis, arms, legs, and feet. Initial evaluation here yielded the following results.

alkaline phosphatase - 1149 calcium - 10.7
phosphate - 3.4
bone scan - extensive increased uptake in many bones
plain radiographs - multiple blastic changes in bones

Since his initial presentation the patient has been treated with intermittent courses of sodium etidronate, salmon calcitonin, or both drugs. Serum alkaline phosphatase and clinical symptoms have both responded somewhat to therapy, however, the patient is never completely chemically normal nor clinically asymptomatic.

These case reports briefly summarize the three most common ways patients with Paget's disease come to the attention of a physician. The first report illustrates the presentation of as many as 40% of patients with Paget's disease; they are asymptomatic. The presence of Paget's disease in these patients serves principally to confuse the physician and often leads to what, in retrospect, were unnecessary evaluations for metastatic cancer or for liver disease. The second case report illustrates a fairly typical presentation of Paget's disease involving a single bone. Such monostotic disease occurs in only about 10% of patients with Paget's disease but is important to recognize since these patients usually have a very gratifying response to treatment. The third case presentation describes a fairly representative patient with symptomatic polyostotic Paget's disease. This is the classic disease described by Paget and rarely presents any difficulty in diagnosis. This type of disease can be progressive and severe and can go on to complete disability. Treatment is useful both to reduce skeletal pain and to treat specific complications of the disease. Treatment of polyostotic disease is rarely totally satisfactory.

Symptoms of Paget's Disease

1. Bone Pain
    a. active bone disease (periosteal stretching)
    b. involvement of joints with exacerbation of osteoarthritis
    c. fissure fractures
    d. complete fractures
    e. gout
    f. pseudogout
    g. osteosarcoma
2. Neurological Dysfunction
    a. deafness
    b. cranial nerve palsies
    c. spinal cord dysfunction
    d. brainstem and cerebellar dysfunction
3. Cardiovascular Dysfunction
    a. increased cutaneous and skeletal blood flow
    b. high output heart failure
4. Other
    a. nephrolithiasis
    b. hypercalcemia
    c. retinal angioid streaks and blindness

Clinical Presentation of Paget's Disease

Paget's disease is an illness principally affecting elderly, white men. Because this patient population generally suffers from arthritis and other chronic ailments, specific symptoms are difficult to elicit. The general state of health of this patient population also partially explains why therapy is not usually totally effective. Only the proportion of the patients' aches and pains caused specifically by Paget's disease can be expected to respond to specific treatment of this disease.

TABLE 26–12. FREQUENCY OF PAGET'S DISEASE AT VARIOUS SKELETAL SITES (% OF PATIENTS)

Site	*Anatomical Studies* (138 Cases)*	*Scintimaging** (108 Cases)*
Pelvis and Sacrum	77	72
Lumbar Spine	50	49
Thoracic Spine		37
Cervical Spine		8
Skull	28	34
Tibia (or Fibula)	8	23
Scapula		18
Sternum	23	
Clavicle	13	7
Radius and Ulna		5
Humerus	4	15
Ribs	7	14
Femur	46	
Miscellaneous		<5

From: Avioli, L.V. and Raisz, L.G. (1980) Bone Metabolism and Disease, in: METABOLIC CONTROL AND DISEASE, Bondy, P.K. and Rosenberg, L.E. (eds.), p. 1784, W.B. Sauders, Philadelphia. (Reproduced with Permission)

The most common symptom of Paget's disease is bone pain (1,2). Bone pain may occur for any one of several reasons. Bone actively involved by Paget's disease simply hurts. Such areas of active involvement may be warm and tender. Paget's disease can involve the bone within joints causing pain because of accelerated or exacerbated arthritis. Patients with this disease are also prone to fractures, either fissure fractures or complete fractures. Fissure fractures are incomplete fractures that occur in Pagetic bone. Most fissure fractures eventually heal. A few, however, go on to become complete fractures. Complete fractures are estimated to occur in about 10% of the total population with Paget's disease and in a much larger proportion of hospitalized patients with this disorder. Such fractures eventually also heal. Other causes of Paget's disease-related bone and joint pain include gout and calcific periarthritis (3). The activity of this disease can be correlated with serum uric acid, suggesting that bone cell turnover in this disease is sufficiently high to make a significant contribution to serum uric acid. It is not known why patients with Paget's disease get calcific periarthritis although it is a common condition occurring in 36% of the patients in one series (3). One rare cause of bone pain should be

mentioned. Patients with Paget's disease are at greater risk of developing osteogenic sarcoma. Such patients are 30-40 fold more likely to develop this rare tumor, however, less than 1% of patients with Paget's disease will eventually be found to have this tumor (1,2,4).

Neurological symptoms are also common in patients with Paget's disease. Deafness occurs in 10-50% of patients and may be caused by eighth nerve compression or by involvement of the boney structures of the middle ear (5). Other cranial nerve palsies occassionally occur (6). Vertebral involvement with Paget's disease can lead to acute cord lesions either because of fracture or extramedullary hematopoiesis with nerve compression or because of vascular steal syndromes (7-9). Skull involvement can cause central steal syndromes and can also cause a flattening of the base of the skull called platybasia. Basilar invagination causes brainstem and cerebellar compression resulting in ataxia, slurred speech, and motor paralysis (1,2,10).

Symptoms related to cardiovascular manifestations of Paget's disease are rare. Skin overlying active lesions and Pagetic bone both demonstrate increased blood flow (11-13). With very extensive skeletal involvement frank high output heart failure can ensue. High output cardiac failure is very rare; most cases of heart failure in patients with Paget's disease are related to organic heart disease, usually atherosclerotic heart disease.

A few other symptoms of Paget's disease should be mentioned briefly. Because bone turnover is so massively increased, sudden immobilization can lead to hypercalcuria and even hypercalcemia. The incidence of nephrolithiasis is increased in patients with Paget's disease (1,14). With fractures and enforced bed rest, frank hypercalcemia may become apparent in patients with extensive skeletal involvement (1). Between 10% and 15% of patients with polyostotic Paget's disease will have angioid streaks. A few of the patients may become blind (15).

A Short Course on Bone Cell Biology Relevant to Understanding Paget's Disease and Its Treatment

To understand Paget's disease, its treatment, and the laboratory parameters followed in patients with this disorder, it is necessary to have at least a superficial knowledge of bone cell biology. Most studies of bone cell biology have focused on two hormonally responsive cells in bone, the osteoclasts and osteoblasts. These two cell types mediate bone responsiveness to parathyroid hormone (PTH), calcitonin, and vitamin D.

Osteoclasts are multinucleated giant cells with receptors for calcitonin (16). The mechanisms by which calcitonin inactivates the osteoclast are not understood completely but are probably dependent on receptor activation of adenylate cyclase. Osteoclasts are unusual cells in that they possess an incredible density of cell surface calcitonin receptors, about 4.8 million per cell (17). These receptors are functionally coupled to adenylate cyclase (17). The dynamics of calcitonin receptor regulation have been studied in some detail either using malignant cells (10) or kidney cells (19,20). These studies indicate that after hormone binds to the cell surface receptor, the resultant complex is internalized in a temperature- and energy-dependent manner. Internalized hormone moves into an acidic compartment, probably the lysosome, where the hormone is degraded (18). Calcitonin treatment of kidney cells results in decreased responsiveness to subsequent rechallenge with calcitonin (19,20). Although calcitonin induces several changes in the receptor cyclase coupling the major reason for hormone-induced hormonal unresponsiveness appears to be recep-

tor down regulation. Several quantifiable post-receptor actions of calcitonin have been detected. In cultures of osteoclast like cells, calcitonin induces cells to round up (11), to stop resorbing bone (22), and to retract carbonic anhydrase from the plasma membrane (23). In kidney cells, calcitonin activates the 25-hydroxylase enzyme (24).

Calcitonin Actions on Osteoclasts

- binds cell surface calcitonin receptor
- activates adenylate cyclase
- hormone receptor complex is internalized in a temperature- and energy-dependent manner
- hormone is degraded in an acidic compartment, probably the lysosome
- acting through what is now just a black box, calcitonin causes osteoclasts to: 1) retract and become round, 2) stop resorbing bone, and 3) shift plasma membrane carbonic anhydrase intracellularly

Osteoblasts are the other major hormone responsive cell type. Autoradiographic studies have localized PTH and vitamin D receptors to the osteoblast. In bone and kidney PTH stimulates the production of cyclic-AMP (25). Cyclic-AMP leads to at least one quantifiable change in cell function. PTH-stimulated osteoblasts secrete more proteases than unstimulated cells (26). Both collagenase and plasminogen activator release are augmented by PTH. Although osteoblasts appear to be the cell type possessing vitamin D receptors, it is not clear what actions vitamin D has on osteoblast function. One of the indicators of disease activity followed in patients with Paget's disease is serum alkaline phosphatase activity. Bone alkaline phosphatase activity comes almost exclusively from osteoblasts. This activity is sufficiently localized to the osteoblast to act as a marker allowing purification of osteoblastic cells from other bone cells.

Bone resorption, an osteoclastic function, is closely coupled to bone formation, an osteoblastic function. At least three examples of cell coupling in bone are known (27). Bone resorption is stimulated by PTH or vitamin D (16). The bone resorbing osteoclasts do not have receptors for either of these hormones, therefore, they must be responding to some other factor or matrix condition produced by a cell with hormone receptors. The alkaline phosphatase values of Pagetic patients treated with calcitonin fall markedly. This occurs despite the fact that the alkaline phosphatase-producing cell, the osteoblast, does not have calcitonin receptors. Recent data from the laboratory of Tim Chambers might help explain at least one of these examples of coupling. His laboratory studies cultures of cells that have characteristics of osteoclasts. These osteoclast-like bone cell cultures round up and quit resorbing bone in response to calcitonin but have no measurable response to PTH (21,22). A small, soluble, heat stable factor released from PTH-stimulated "osteoblasts" confers PTH responsiveness on the "osteoclasts" (28). Thus, it would seem likely that PTH responsiveness of osteoclasts is indirect and requires the mediation of the osteoblast. It seems quite possible that osteoclast response to vitamin D and osteoblast response to calcitonin might be mediated by similar cell message molecules. Because the activities of bone cells are coupled drugs affecting one cell type may have indirect influences on other cells. Thus, a treatment that decreases bone resorption in Paget's disease could do so by directly inhibiting osteoclast function, by inhibiting osteoblast function, or by some other totally unrelated mechanism.

TABLE 2. Resorption of bovine cortical bone slices by osteoclasts in the presence and absence of PTH (10^{-1} U/ml) and UMR cells, and the effects of supernatants from these cultures on fresh populations of disaggregated osteoclasts

	Pits/bone slice	Mean pit surface area/bone slice ($\mu m^2 \times 10^{-3}$)	Bone resorption/ bone slice ($\mu m^2 \times 10^{-3}$)
OC	3.8 ± 0.8	1.4 ± 0.3	5.8 ± 1.3
OC + PTH	5.3 ± 1.1	0.8 ± 0.1	5.1 ± 1.1
OC + UMR	3.6 ± 0.9	1.6 ± 0.3	7.1 ± 1.9
OC + UMR + PTH	11.7 ± 2.1	1.7 ± 0.3	26.3 ± 7.6
S (OC)	8.6 ± 1.8	1.5 ± 0.2	13.2 ± 2.2
S (OC + PTH)	10.0 ± 2.2	1.9 ± 0.5	14.9 ± 4.8
S (OC + UMR)	7.3 ± 2.0	2.1 ± 0.4	13.9 ± 6.1
S (OC + UMR + PTH)	20.8 ± 5.9	1.4 ± 0.2	27.7 ± 6.8

Results are expressed as the mean ± SEM of five consecutive experiments (five bone slices per group in each experiment). S (OC + UMR + PTH), Resorption by osteoclasts cultured in the presence of supernatant from cultures of osteoclasts with UMR cells and PTH (mean number of osteoclasts per bone slice: first incubation, 4 ± 1; second incubation, 5 ± 1).

From: McSheehy, P.M.J. and Chambers, T.J. (1986) Osteoblast-like Cells in the Presence of Parathyroid Hormone Release Soluble Factor that Stimulates Osteoclastic Bone Resorption. Endocrinology 119:1654 (Reproduced with permission)

Some of the components of bone matrix must be mentioned briefly. Most of bone mass is matrix mass. The bone matrix is made up of 35% organic material, mainly collagen, and 65% inorganic material, mainly hydroxyapatite. The organic portion of bone furnishes two markers of bone turnover. Collagen contains virtually all of the hydroxyproline and hydroxylysine in the body, and the bulk of collagen is in the bone. Therefore, urinary hydroxyproline excretion is a good marker of bone turnover, both bone resorption and formation. A trace component of bone, osteocalcin or bone GLA protein, is released into serum and can be quantitated. This 6000 MW peptide increases in serum under conditions of increased bone turnover (29). Bone mineral calcium and phosphate is arranged mainly into large crystals of hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$. Hydroxyapatite has a very large surface to volume ratio that apparently facilitates calcium and phosphate flux. The hydroxyapatite crystal also has a very high binding affinity for pyrophosphate or the pyrophosphate analogues, the diphosphonates (30). Selective concentration of diphosphonates in bone limits toxicity to bone cells or cells in close proximity to bone (27).

Pathology and Laboratory Abnormalities

Paget's disease is characterized by massive bone resorption coupled to usually equally massive bone formation (31). The primary lesion is thought to involve the osteoclast. This conclusion is based on microscopic studies that have shown bone resorption to be most active in early Pagetic lesions while bone formation tends to predominate in older lesions (32,33). This conclusion is buttressed by the not rare finding of isolated lytic Pagetic lesions. Regardless of the primarily affected cells the pathological appearance and biochemical presentation are usually results of both excessive bone resorption and formation.

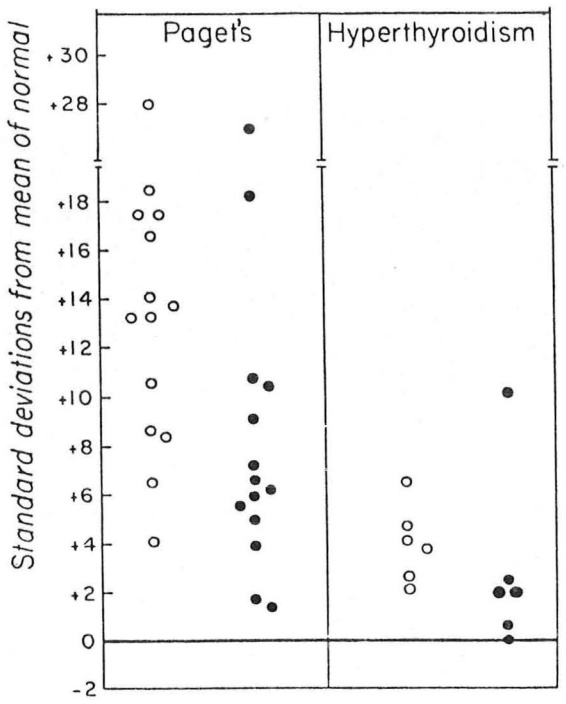


FIGURE 20–133 Microradiographic determination of bone turnover, resorption (open circles) and formation (closed circles) in Paget's disease and hyperthyroidism. Although there is excessive bone turnover in both diseases, available data emphasize the extraordinary degree of abnormality in Paget's disease; bone resorption in one third of the patients is sixteen- to twenty-eightfold higher than normal.

From: Jowsey, J. (1966) Quantitative Microradiography: A New Approach to the Evaluation of Metabolic Bone Disease. Amer. J. Med. 40:485 (Reproduced with Permission)

The microscopic appearance of Pagetic bone is extremely characteristic and can be differentiated from normal bone even on low power examination (34). Bone affected by Paget's disease shows evidence of excessive osteoclastic attack and evidence for disordered and excessive reformed bone. This bone contains numerous punched-out and apparently random osteoclast attack sites. Cement lines become prominent and intersect at odd angles. This finding as well as the disordered filament structure of Pagetic bone is most noticable when viewed under polarized light. The most obvious and characteristic microscopic changes in Paget's disease are the changes of excessive disordered bone deposition. Only in very early lesions will the primary resorptive osteoclastic lesion predominate.

Microscopic Appearance of Pagetic Bone

- increased cellularity
- mosaic bone pattern
- fibrous marrow

Laboratory findings in patients with Paget's disease also reflect the excessive bone turnover. Serum GLA protein is elevated (30) as is urinary hydroxyproline excretion (35). Both laboratory abnormalities reflect the sum of increased bone destruction and reformation. Serum calcium and phosphate are usually normal in Paget's disease (1), a finding that tends to reinforce the impression that bone reformation fairly well matches bone destruction. Serum alkaline phosphatase values are typically elevated in Pagetic patients (36) and reflect the excessive bone formation characteristic of the reactive portion of the disease. Patients with very early or purely lytic disease can have elevated urine hydroxyproline values without any detectable elevation in serum alkaline phosphatase. Such patients must be quite rare, however, since both urine hydroxyproline and serum alkaline phosphatase correlate equally well with extent of skeletal involvement (3).

Laboratory Abnormalities of Paget's Disease

Increased - serum alkaline phosphatase
- urine hydroxyproline
- serum GLA protein (osteocalcin)
- serum Type I procollagen

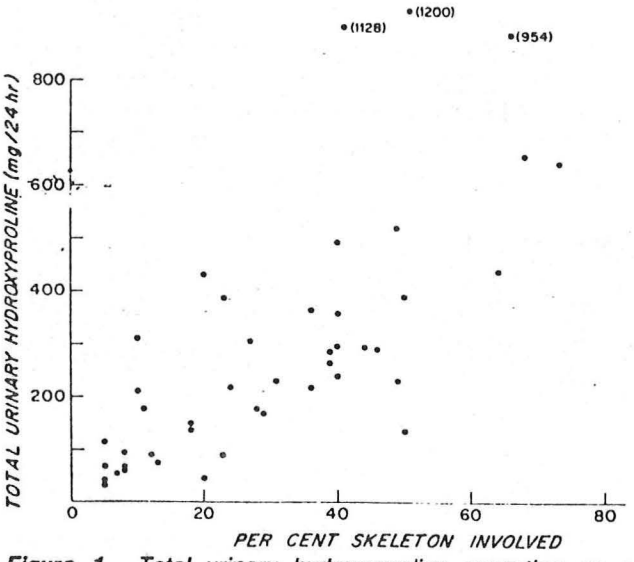


Figure 1. *Total urinary hydroxyproline excretion as a function of extent of Paget's involvement of bone.*

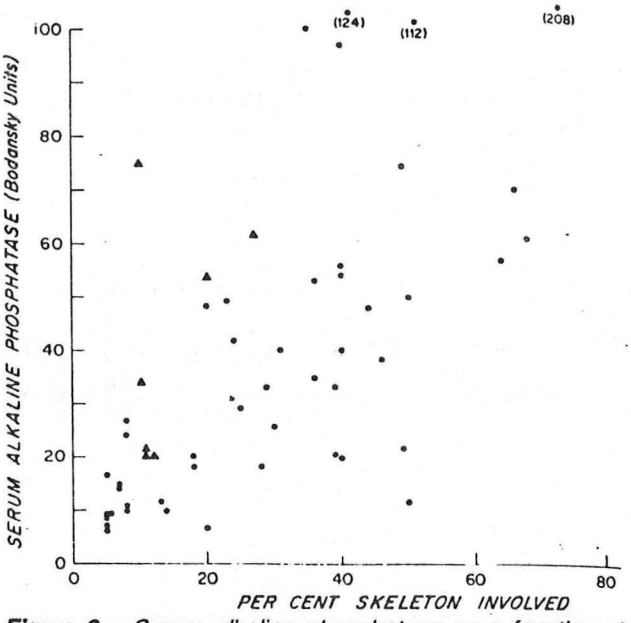


Figure 2. *Serum alkaline phosphatase as a function of Pagetic involvement of bone. Patients with skull disease predominantly and unusual elevations of serum alkaline phosphatase levels are indicated by (▲).*

From: Franck, W.A., Bress, N.M., Singer, F.R., and Krane, S.M. (1974) Rheumatic Manifestations of Paget's Disease of Bone. Am. J. Med. 56:592 (Reproduced with Permission)

The typical radiographic and bone scan findings of patients with Paget's disease also reflect both excessive bone resorption and deposition. The blastic lesions characteristic of reactive bone formation tend to dominate the radiographic picture. By radiographic appearance alone these changes cannot be differentiated from blastic, metastatic lesions. Lytic Pagetic lesions are sometimes seen near or advancing in front of blastic lesions. One lytic lesion, osteoporosis circumscripta, is pathognomonic for Paget's disease. Other characteristic X-ray findings of Paget's disease include widened dense vertabrae, blastic disease ending sharply at the end of bones or at suture lines, disease sharply demarcated to one half of the pelvis, and alternating blastic and lytic disease. The finding of longstanding widespread blastic lesions in the face of minimal clinical symptoms is very typical for Paget's disease. Bone scans generally show the same lesions as plain X-ray films. There are, however, some exceptions. Bone scans tend to preferentially demonstrate new and active lesions. Old sclerotic lesions may not show up on bone scan. Although very sensitive, bone scans do not differentiate blastic from lytic lesions, so plain films may still be required.

Etiology of Paget's Disease

The best evidence presently available suggests that Paget's disease is caused by viral infection and that genetic susceptibility to infection may explain familial cases of Paget's disease. Paget's disease is distributed very asymmetrically around the world (2). This disease tends to be most common in central Europe, the United Kingtom, Australia, and New Zealand but is also found at a lower incidence in southern Europe, Scandinavia, and in the United States. Paget's disease is more common in the northern than the southern United States and is rare in China, Japan, the Middle East, India, and Africa. Paget's disease can occur with different frequencies in two cities in a single geographic area (1,37). Heredity must have a role in some cases of Paget's disease since clear-cut familial transmission has been documented frequently (38). Most cases of Pagets disease are sporadic, however, and the striking geographic clustering has suggested an infectious etiology. Research groups in France and the United States have identified nuclear viral inclusions in osteoclasts from patients with Paget's disease (39,40). The putative virus has not yet been identified. These initial reports have shown, however, that the inclusions are specific and are not found in the osteoclasts of normal patients or patients with other bone diseases. There is no evidence indicating that chronic inflammatory disease, vascular disease, disease of collagen synthesis, or primary hormonal disease underlie any cases of Paget's disease.

Etiology of Paget's Disease

- familial clustering
- geographic clustering
- nuclear viral like particles in osteoclasts

Treatment Rationale and Treatment Options

Two moderately specific treatments have been successfully used to treat Paget's disease. Both the hormone, calcitonin, and the class of drugs known as diphosphonates cause clinical and chemical improvement. As presently used, each treatment has some significant drawbacks and therapeutic advantages.

Rationale - Calcitonin

Calcitonin, the drug, presumably acts through the same receptors as does the physiological hormone. Calcitonin probably acts directly on the overactive osteoclasts characteristic of Paget's disease. Because of coupling of osteoclastic and osteoblastic function in this disease, evidence of osteoblastic overactivity (serum alkaline phosphatase) decreases as much as urine hydroxyproline. It seems unlikely that calcitonin actions on kidney or other cells (41) are required for the treatment response of Pagetic patients to calcitonin.

There is considerable clinical experience with porcine, human, and salmon calcitonin. The salmon hormone is the most potent of any of the known and characterized hormones (42), but like any nonhuman hormone, it can induce allergic reactions. Generally, these are cutaneous reactions, but occassional patients have been reported with drug resistance believed to have been caused by anticalcitonin antibodies (43-45). Calcitonin has generally been administered by subcutaneous injection, however, recent data have clearly shown that the drug can be absorbed through mucous membranes (46). Data on this latter route of administration are so limited, however, that today's discussion will center on studies using subcutaneously injected calcitonin.

Treatment of Paget's Disease with Calcitonin

There are a number of questions that must be asked of any drug used to treat Paget's disease: 1) will the drug result in clinical and chemical remissions in short term trials, 2) can these remissions be sustained, and will radiographic healing of affected bones occur, 3) can any of the rare but serious complications of Paget's disease be reversed or prevented entirely by treatment. This latter question will be discussed in detail under "Discussion of Treatment Effects on Specific Complications". Two more questions are specifically relevant to calcitonin therapy since such therapy employs an expensive synthetic peptide that must be injected. 4) what is the minimum dosing schedule that can be expected to be effective, and 5) can remissions be maintained off of therapy.

1) Short term efficacy of calcitonin - By now many studies have shown biochemical and clinical improvement of patients with Paget's disease who have been treated with calcitonin (47-50). In most studies maximal response to calcitonin is incomplete. In general, patients with the most strikingly abnormal lab values sustain the greatest absolute response but the smallest percent response. On average, urinary hydroxyproline and serum alkaline phosphatase decrease by 40%-60% of the baseline, pretreatment values. Clinical symptoms may respond quite dramatically but rarely disappear completely. Calcitonin treatment responses are also very fast. A recent study has shown that type I procollagen, an extremely sensitive indicator of bone disease, decreases within hours of calcitonin injection (51). Such levels do not respond until after weeks of oral diphosphonate treatment. These latter data provide the rationale for including calcitonin in treatment regimens requiring a rapid onset of action.

2) Sustained remissions and radiographic healing - The ability of calcitonin to sustain a remission is somewhat controversial. Several facts appear well established, however. Biochemical tests of disease activity do not remain maximally suppressed for long periods of time. Usually during calcitonin therapy serum alkaline phosphatase and urine hydroxyproline decrease to minimal values within a few weeks and then tend to drift back toward pretreatment values. This plateau or escape effect and has been rather intensely studied. Possible explanations for this phenomenon include: a) anticalcitonin neutralizing antibodies, b) secondary hyperparathyroidism, and c) cellular desensitization to calcitonin.

Although antibodies that bind and neutralize salmon and porcine calcitonins have been described in calcitonin refractory patients (43-45), it seems that these antibodies cannot explain all cases of calcitonin resistance (45). In some patients the presence or absence of antibodies does not correlate in a specific manner with disease progression or biochemical relapse (52). Although secondary hyperparathyroidism could conceivably be induced by chronic calcitonin therapy, such a condition has not been found in practice. Most investigators believe that cellular refractoriness or desensitization to calcitonin underlies many cases of this phenomena (45). This thinking is based on in vitro experiments that have demonstrated calcitonin-induced calcitonin unresponsiveness in either bone (53) or kidney cells (19,20). Although this explanation is plausable, there is no direct proof of its existence in intact humans. Iain MacIntyre and his collegues in London have advanced an idea quite different from the three discussed so far (54). These investigators argue that there actually is no plateau or escape involving calcitonin action on Pagetic bone and that the observed rebound in biochemical parameters occurs because of bone healing. Their argument is based on three lines of evidence. First, they argue that clinical relapse does not reproducibly follow biochemical relapse. Secondly, they argue that alkaline phosphatase and hydroxyproline measurements cannot differentiate between bone healing and relapse of Paget's disease. Finally, they state that they have seen healing of bone lesions in patients experiencing biochemical plateau or relapse.

Causes of Calcitonin Resistance

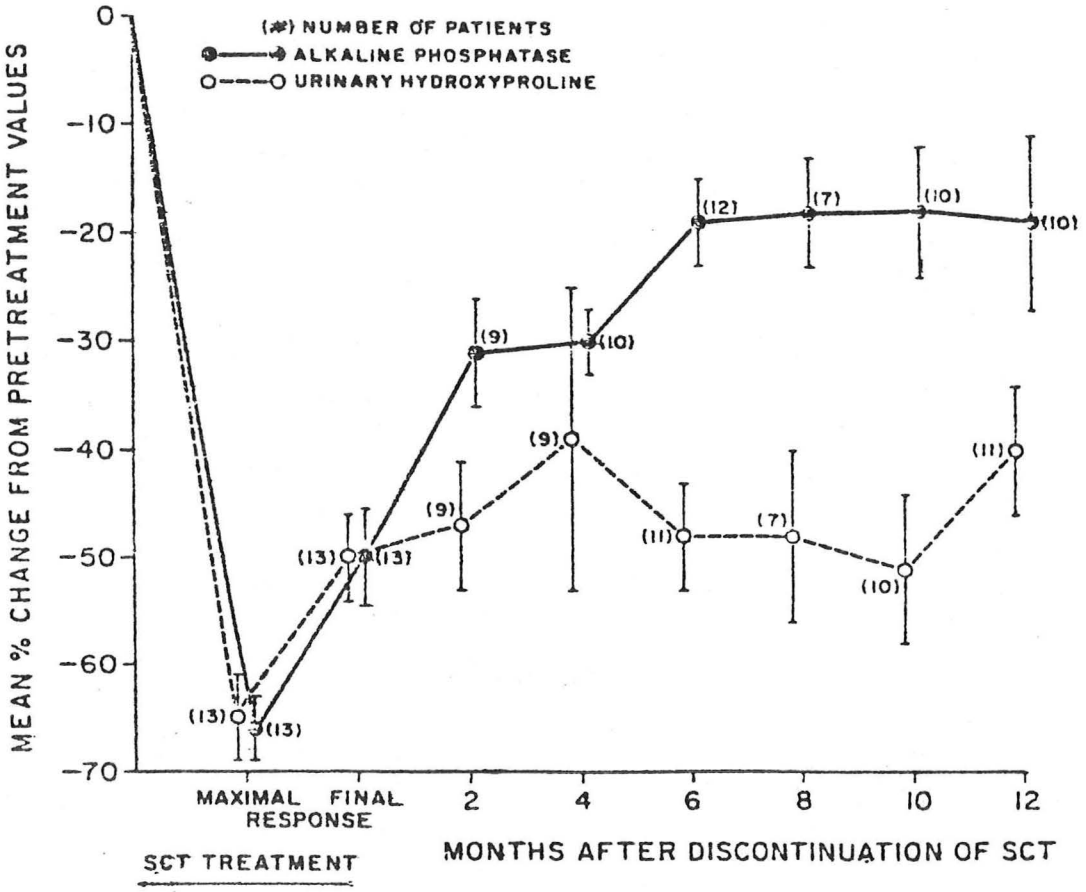
- neutralizing antibodies
- target cell desensitization
- calcitonin resistance does not exist

Radiographic healing of Pagetic bones has been documented after treatment with human calcitonin (54-57). Although the human hormone was used for all of these cases, it is probable that porcine or salmon calcitonin would also have been effective. All authors make a particular point of recommending calcitonin for the treatment of the lytic phase of Paget's disease. In the United States this recommendation makes particular sense because the only diphosphonate approved for humans is etidronate disodium, a diphosphonate that inhibits bone mineralization.

3) Treatment of serious complications of Paget's disease with calcitonin - Calcitonin has been shown to be effective treatment for a number of complications of Paget's disease. The treatment of specific complications will be discussed below.

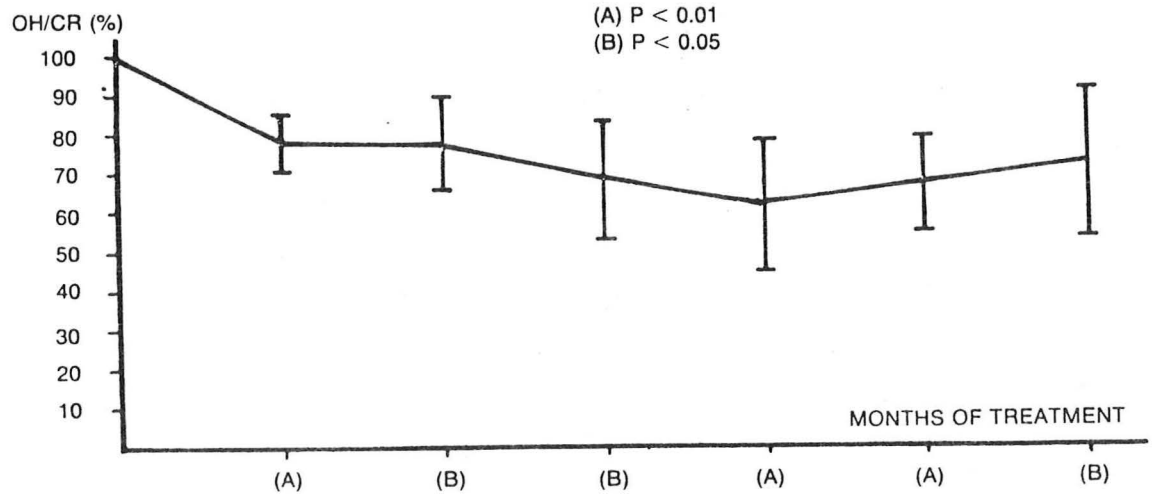
4) Minimum dosing schedule - Since calcitonin is a peptide hormone it is moderately expensive. The cost of calcitonin to the United States government is $6.75 per 50 Medical Reserach Council units (M.R.C.U.), and the costs to the patient at two local discount pharmacies were $7.75/50 M.R.C.U. and $9.00/50 M.R.C.U. At these prices, drug cost becomes a significant issue; many patients will elect bone pain rather than bankruptcy. Studies of calcitonin effectiveness have employed doses ranging from 50 M.R.C.U. given three times per week (45) to 200 M.R.C.U. given each twelve hours (48). The absolute minimum cost of these treatments would be $81.00/mo. at the low dose and $1,540/mo. at the high dose. Fred Singer, one of the authors employing low dose calcitonin, admits that 50 M.R.C.U. three times per week is not always effective. In the case of disease not responding to this dose of calcitonin, Dr. Singer increases the dose to 50 M.R.C.U. or 100 M.R.C.U. daily. These doses are more average doses and would cost the patient at minimum $189.00 and $378.00 each month, respectively.

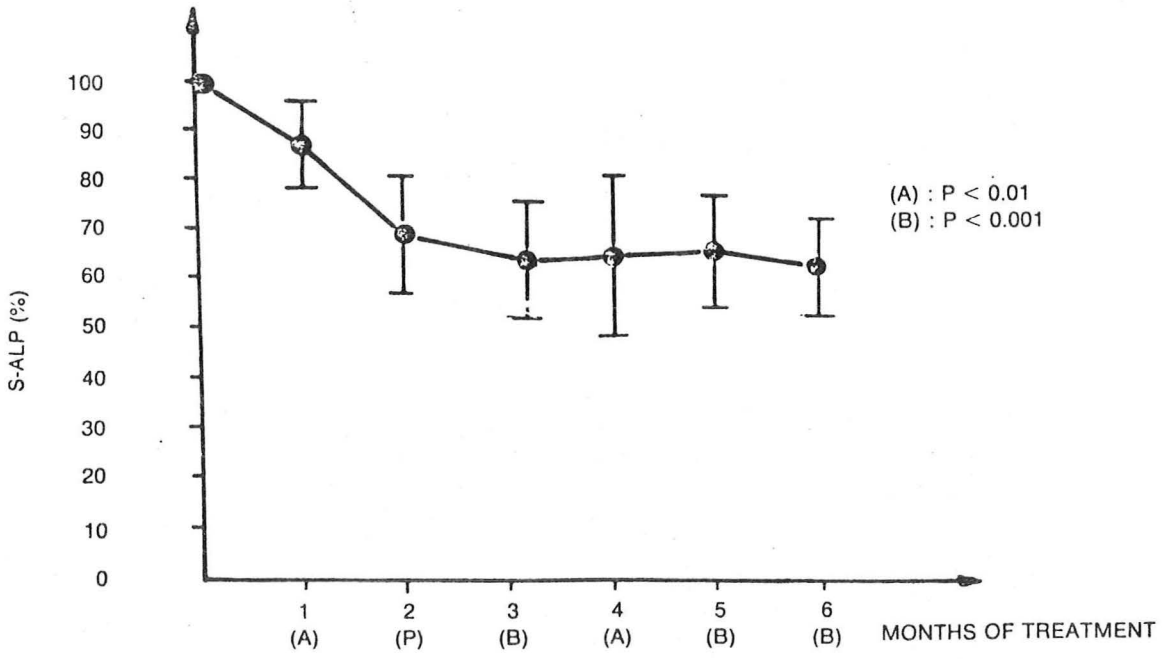
5) Long term remissions - One factor acting to significantly lower the cost of calcitonin therapy is the occurrence of prolonged clinical remissions after stopping calcitonin therapy. Both clinical and biochemical remissions have been maintained for variable lengths of time (58,59). Avramides and coworkers documented a continued state of clinical remission in ten of thirteen patients studied after discontinuing various doses of calcitonin (59). In this study, plasma alkaline phosphatase values increased quite markedly within six months of stopping therapy while urine hydroxyproline secretion remained unchanged for more than one year. Two patients required retreatment because of recurrence of bone pain at three and four months, respectively. One patient had recurrence of neurological complications at ten months after discontinuing calcitonin. Iain MacIntyre and coworkers have now followed a group of patients for as long as 32 months following discontinuance of calcitonin therapy. These authors found that 16 of 27 patients remained in clinical remission after this period of time. Interestingly, in this group of patients, no biochemical parameter remained suppressed for prolonged times after stopping therapy. It was also of interest that the biochemical responses of patients requiring retreatment did not seem significantly different than the responses of patients that remained in remission. Patients required retreatment in this study either because of major orthopedic surgery (two patients) or because of clinical and radiographic recurrence (eleven patients). These authors recommend retreatment with calcitonin at the dose of 100 M.R.C.U. twice a week for clinical relapse or 100 M.R.C.U. daily for radiological relapse.



From: Avramides, A., Flores, A., DeRose, J., and Wallach, S. (1976) Paget's Disease of Bone: Observations after Cessation of Long Term Synthetic Salmon Calcitonin Treatment. J. Clin. Endocrinol. Metab. 42:459 (Reproduced with Permission)

It should be mentioned that suppression of biochemical parameters may be achieved by nasal inhalation of calcitonin (46). At doses of 200 M.R.C.U. or 400 M.R.C.U. each day, serum alkaline phosphatase values decreased about 35% while urine hydroxyproline values decreased about 15%. Clinical symptoms improved as well. One of the five patients showed radiographic progression on treatment, and in all patients biochemical suppression was less than the suppression achieved at much lower doses of calcitonin administered subcutaneously.

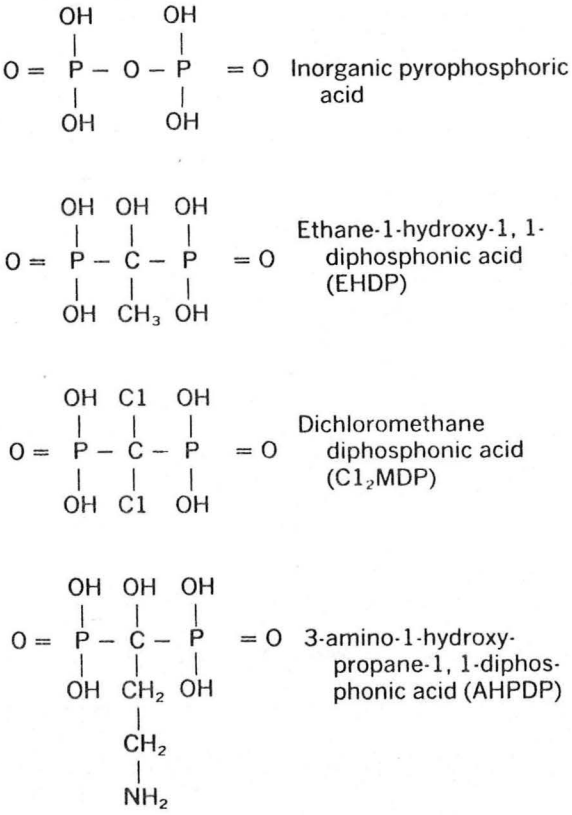




From: Reginster, J.Y., Albert, A., and Franchimont, P. (1985) Salmon-calcitonin Nasal Spray in Paget's Disease of Bone: Preliminary Results in Five Patients. Calcif. Tiss. Int. 37:577 (Reproduced with Permission)

Diphosphonates

The diphosphonates are pyrophosphate analogues. Pyrophosphates have been known to chemists for many years and have industrial applications as anti-scaling compounds for boilers and pipes (60,61). These compounds inhibit the deposition of calcium carbonate from solutions but have few effects in intact animals since they are rapidly destroyed by pyrophosphatases. Diphosphonates differ from pyrophosphate in that they have a carbon-phosphate bond instead of an oxygen-phosphate bond. The carbon substitution makes diphosphates resistant to hydrolysis so that the analogues can be effective in animals or man.



From: Fleisch, H. (1980) Experimental Basis for the Clinical Use of Diphosphonates in Paget's Disease of Bone. Arthritis and Rheum. 23:1162

The chemical properties of diphosphonates account for their usefulness as nuclear medicine tracers and for a portion of their usefulness as drugs. Because diphosphonates have very high binding affinity for hydroxyapatite crystals, they are very selectively concentrated in bone (63). Virtually all ingested diphosphonates will either be eliminated from the body or concentrated in bone. This characteristic makes diphosphonates excellent bone scanning agents. The very selective concentration in bone also tends to limit toxicity to bone cells or cells close to bone. Diphosphonates inhibit calcium deposition into biological tissues (63). This property has been exploited clinically in the treatment of hypertrophic calcification. One other physical property of diphosphonates is of interest. Diphosphonate-treated calcium salts go into solution less well than untreated salts (63). This latter characteristic of diphosphonates was at one time thought to account for their ability to block

bone resorption. At the present time this mechanism is felt to be unimportant, and most research interest has shifted to cellular effects of diphosphonates.

Diphosphonates have a number of effects on cellular metabolism (64-70). It is clear that diphosphonates are taken up by cells and distributed mainly in the cell cytoplasm (71). Since these drugs are so concentrated in bone, mainly bone cells take up the diphosphonates. Diphosphonates block glycolysis (64,65), stimulate β-oxidation of fatty acids (66) and the Krebs cycle (67,68), and inhibit prostaglandin synthesis (69,70). None of these metabolic effects of diphosphonates correlates well with their ability to block bone resorption. Some metabolic changes, most noticably inhibition of prostaglandin synthesis, may in fact be stimulated by diphosphonates that are quite active in inhibiting bone resorption (70).

Diphosphonates can act as cytotoxic agents. The appearance of bone cell hypoplasia has been documented in diphosphonate treated animals and man (72-74). The treated bones demonstrate morphologic abnormalities in all cells but show preferential effects on osteoclasts. Selective cytotoxicity for osteoclasts, whether mediated by a known metabolic effect of diphosphonates or an effect yet to be discovered, would be an attractive mechanism to explain diphosphonate inhibition of bone resorption. This has not proven easy to demonstrate, however. Like most other characteristics of diphosphonates, cytotoxicity demonstrated in cultured cells does not correlate well with the ability of that diphosphonate to inhibit bone resorption (75). It is possible that the failure to demonstrate such a correlation is artifactual. It is not at all clear that the chronic toxicity seen in diphosphonate treated animals is comparable to the relatively acute toxicity demonstrable in vitro. It is also possible that cytotoxicity is a variable side effect of various diphosphonates and is unrelated to the critical effect that is responsible for blocking bone resorption.

Diphosphonate-mediated cytotoxicity is not limited to bone cells. The growth of cultured macrophages can be inhibited by diphosphonates; diphosphonate bound to bone is more effective than free diphoshonate (76). Diphosphonates can inhibit mitogen stimulated lymphocyte proliferation (77). High concentrations of dichloromethylene bisphosphonate given to young mice induce an osteopetrosis-like syndrome and lead to depletion of natural killer (NK) lymphocytes (78). The NK cells are important in that they police for malignant hematologic cells. All of these studies taken together suggest that diphosphonates may be toxic to other cells located near bone. These studies raise at least the theoretical possibility that chronic diphosponate use could lead to excess hematologic malignancies. Thus far, no such association has been established. It is quite possible that the lower doses and intermittent treatment schedules employed in patients may minimize or even eliminate any significant effects of diphosphonates on the immune system.

Chemical Properties of Diphosphonates

- strongly bind to hydroxyapatite
- inhibit calcium deposition in tissue
- inhibit crystal dissolution in vitro

Cellular Actions of Diphosphonates

- inhibit glycolysis
- stimulate β-oxidation of fatty acids
- stimulate Krebs cycle activity
- inhibit prostaglandin synthesis
- kill cells

Cytotoxicity of Diphosphonates

- demonstrated for cultured bone cells
- altered morphology and decreased numbers of bone cells found in diphosphonate-treated animals
- toxicity for macrophages in vitro
- depressed immune function and immune mediator cells from diphosphonate treated animals

Treatment of Paget's Disease with Diphosphonates

In evaluating the efficacy of diphosphonates as drugs useful for treating Paget's disease, it is helpful to attempt to answer the same five questions asked for calcitonin treatment of Paget's disease. These questions are slightly more complex in this case since several diphosphonates have been employed clinically, and each diphosphonate can have somewhat different toxicity and clinical potency. In my discussion today I will generally be concentrating on data using disodium etidronate (EHDP), the only diphosphonate presently available in the United States. I will mention some data obtained using dichloromethylene diphosphonate (Cl_2MDP), a diphosphonate tested in the United States but not approved. I will at least briefly mention one other drug (3-amino-1-hydroxypropylidene)-1-bisphosphonate (ADP), a diphosphonate that has been extensively studied in European trials.

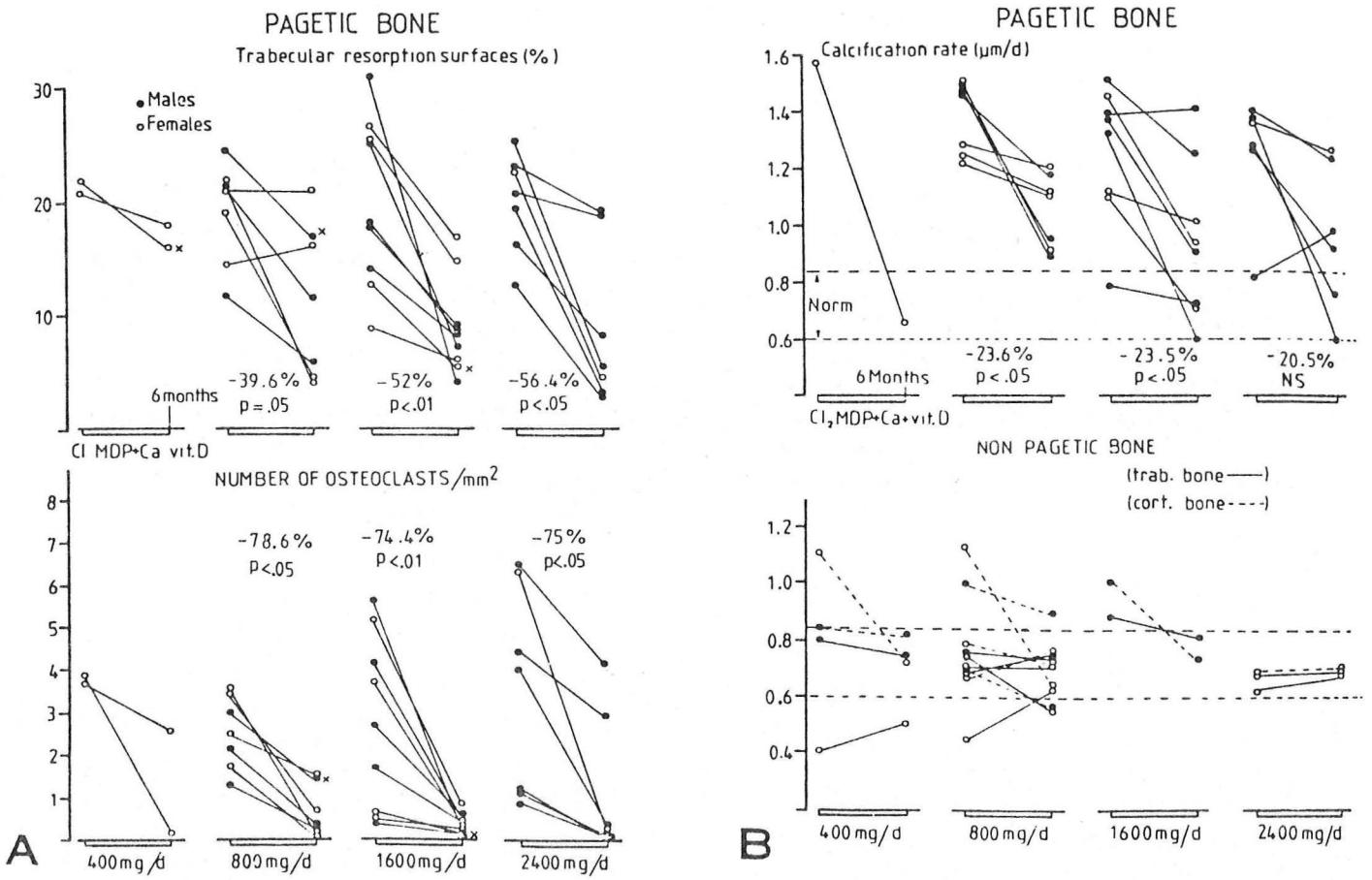


FIG. 4. Bone histology. Changes in histomorphometric parameters as measured in pagetic and nonpagetic iliac bone biopsy specimens after 6 months of Cl_2MPD, calcium, and vitamin D therapy.

From: Delmas, P.D., Chapuy, M.L., Vignon, E., et al. (1982) Long Term Effects of Dichloromethylene Diphosphonate in Paget's Disease of Bone. J. Clin. Endocrinol. Metab. 54:837 (Reproduced with Permission)

Short Term Remissions with Diphosphonates

EHDP - The first study to demonstrate efficacy of a diphosphonate in treating the biochemical abnormalities characteristic of Paget's disease was that of Smith and coworkers published in the Lancet in 1971 (79). These authors used what in retrospect is a large dose of EHDP, 20 mg/kg body weight/day. Treatment with EHDP at this dose resulted in lowering both urinary hydroxyproline excretion and serum alkaline phosphatase values by or before twelve weeks. This initial study carefully avoided any strong statements relating drug treatment to relief of pain. Two years later these authors expanded this initial report (31). In the new report more patients were studied, and bone biopsy results were given. Although the post treatment biopsies were taken after various treatment intervals and at various times after treatment, they all showed two characteristic features. The biopsies from EHDP treated patients showed decreased numbers of bone cells and increased nonmineralized osteoid. Both osteoclasts and osteoblasts were reduced in both normal and Pagetic bone. The authors noted that osteoclasts in treated patients looked "inactive". This study was the first evidence that EHDP would cause a mineralization defect in humans. A study by Bijvoet and coworkers at the same time indicated that this mineralization defect may be dose related (80). These authors found that doses of EHDP up to 10 mg/kg body weight/day could be used for up to six months without any histological evidence of mineralization defect. Both of these studies reported reduction in pain, but neither were placebo controlled. Calcium balance remained negative in three of four patients treated with EHDP at 20 mg/kg/day. The first double-blind trial of EHDP therapy was reported by Altman and coworkers shortly after these studies (81). These investigators used doses of EHDP ranging from 1 to 20 mg/kg/day and showed dose dependent suppression of urinary hydroxyproline and serum alkaline phosphatase values. They also found a significant dose dependent alleviation of pain. Almost 33% of their patients had a pain response to placebo. At the highest EHDP dose tested six of seven of the patients (86%) had a favorable response. These authors noted that long bone pain was more likely to respond than pain near a joint. Since that time, a number of studies have quite adequately confirmed these results.

Three potential problems are encountered when EHDP is employed for the treatment of Paget's disease. The first is the mineralization defect induced by EHDP. This effect of the diphosphonate is dose dependent and can generally be minimized by using EHDP at doses less than 10 mg/kg/day for less than six months. Two other problems deserve attention. Some but not all authors feel that EHDP should not be used for lytic Paget's disease since this drug might cause worsening of such disease. Using serial radiographs of long bone, Nagant de Deuxchaisnes and coworkers found that EHDP at the relatively low dose of 6.7 mg/kg/day caused osteolytic lesions to increase (86). This study is of particular interest since the same authors using identical techniques found that calcitonin healed such lesions (87). This latter finding now has been widely reproduced and is in agreement with the experiences of most other investigators (55-58). These authors also showed that calcitonin could cure EHDP-induced/-worsened osteolytic lesions. Krane, in reviewing EHDP treatment of Paget's disease, states that he has seen findings similar to those of Nagant de Deuschaisnes (88) while Murphy and coworkers report healing of osteolytic lesions with EHDP therapy (89). At the most recent Endocrine Society meeting, J.A. Kanis showed two examples of osteolytic lesions that were presumably healed with EHDP therapy (90). Fracture rates would tend to reinforce the idea that EHDP worsens lytic disease but here again, the data is not unequivocal. Kantrowitz and coworkers found a very high rate of fracture in EHDP treated patients (91). These authors' patients experienced no fractures in the 18 months preceding therapy and then ten fractures in 20 patients during therapy. The fractures tended to be at the site of osteolytic Paget's disease and

occurred in patients taking either 10 or 20 mg/kd/day of EHDP. Finerman and associates reported fractures in four of 21 patients treated with 20 mg/kg/day EHDP for six months (92). Ibbertson and coworkers also found what they believed to be excess fractures occurring in patients treated with 20 mg/kg/day EHDP (93). Both Khairi and coworkers and Canfield and associates found fractures associated with EHDP therapy. Neither group was willing to attribute the fractures unequivocally to EHDP therapy, and both groups found a far lower incidence of fractures than did Kantrowitz and coworkers. Several groups have noted that pain at the site of Pagetic lesions tends to limit therapy in some patients (84,85,91,94). It is not clear whether this complication is strictly dose related or why it occurs at all.

In the sixteen years that EHDP has been used clinically, a consensus has more or less been reached about how to use it. High dose EHDP (20 mg/kg/day) is not used for more than one month. The one month time span is set to limit the chance of significant osteomalacia and reduce the chance of fracture. This dose can significantly improve the biochemical abnormalities of Paget's disease and can lead to clinical improvements (81,95). Longer term therapy lasting up to six months employs doses of EHDP ranging from 5-10 mg/kg/day. Lower dose diphosphonates probably do not block biochemical disease so well but are less toxic. Average results using EHDP treatment are shown below. Generally, it is expected that this treatment should result in sustained suppression of biochemical indicators of disease to about 50% of pretreatment values.

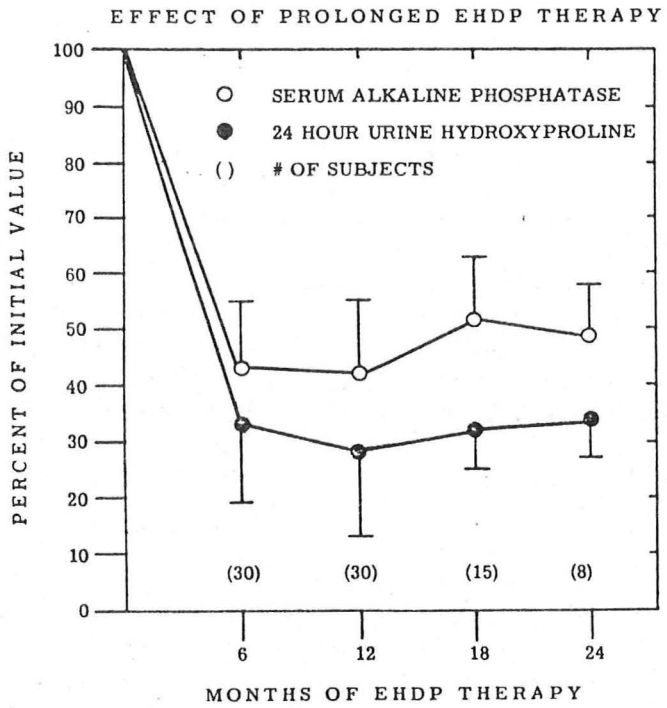
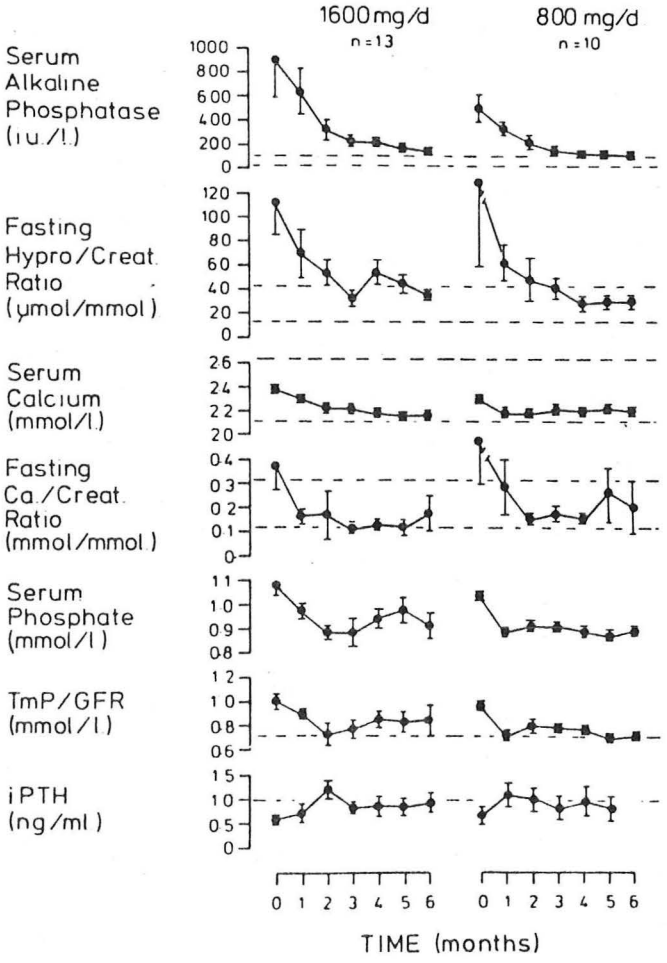


Figure 2. Changes in serum alkaline phosphatase and urinary hydroxyproline expressed as percent of initial value (mean ± SEM) after 6, 12, 18, or 24 months of sodium etidronate (EHDP) therapy (5, 10, or 20 mg/kg body weight · day).

From: Khairi, M.R.A., Altman, R.D., DeRosa, G.P., et al. (1977) Sodium Etidronate in Treatment of Paget's Disease of Bone, A Study of Long Term Results. Ann. Intern. Med. 87:656 (Reproduced with Permission)

Other diphosphonates - Both dichloromethylene diphosphonate (Cl_2MDP) and (3-amino-1-hydroxypropylidine)-1,1-bisphosphonate (APD) have been used to successfully treat patients with Paget's disease (96-100). These diphosphonates are not currently available in the United States but have been used extensively in Europe. Both of these diphosphonates differ from EHDP in that they do not induce a significant calcification defect. Because of this difference it is possible to employ more efficacious doses for longer periods of time without the risk of osteomalacia or fracture. This more biochemically effective therapy may be accompanied by secondary hyperparathyroidism that may in turn require treatment with calcium and vitamin D (100). Although it has not been encountered clinically therapy with more potent diphosphonates could exert significant effects on immune policing for hematologic malignancies (76-78). It should also be pointed out that the greater efficacy of these second generation diphosphonates in suppressing biochemical parameters of disease does not necessarily translate into greater clinical efficacy.



From: Douglas, D.L., Duckworth, J.A., Kanis, C., et al. (1980) Biochemical and Clinical Responses to Dichloromethylene Diphosphonate (Cl_2MDP) in Paget's Disease of Bone. Arthritis and Rheum. 23:1185 (Reproduced with Permission)

2) Sustained remissions and radiographic healing - All of the diphosphonates thus far studied can lead to sustained remissions. Unlike calcitonin there is no "biochemical escape" from diphosphonate therapy. As long as diphosphonate is present in bone (and it does not leave bone rapidly or easily), there will be continued effects on bone resorption and/or bone mineralization.

Radiographic healing with EHDP therapy was discussed above. The data indicating that EHDP will cause healing of radiographic bone disease is far less convincing than the data for calcitonin. High dose EHDP may increase fracture incidence, a finding quite consistent with the worsening of radiographic disease seen by some investigators. Fracture incidence is said not to increase with either Cl_2MDP or ADP therapy (98,99). I was unable to find published documentation that either drug could cause healing of lytic lesions.

3) Rare life-threatening complications - Diphosphonate therapy will be discussed with calcitonin therapy in a separate section below.

4) Minimum effective doses - The upper limit for dosing EHDP is set by toxicity. Many authors feel that higher EHDP doses produce better clinical and biochemical responses, however, the careful study of Canfield and coworkers (85) as well as the experience of Krane (88) do not agree with this view. Almost all authors agree that 5 mg/kg/day of EHDP is an effective dose. In Canfield's study where dose response data were clearly worked out, 20 mg/kg/day of EHDP was probably more effective in suppressing biochemical parameters of disease than lower doses. At doses between 2.5 and 10 mg/kg/day of EHDP biochemical responses were equivalent. Clinical responses in this series were actually better at the lower doses of EHDP since a number of patients taking the 20 mg/kg/day dose developed bone pain. It is possible that very short term high dose oral (95) or intravenous EHDP therapy (101,102) may maximize treatment effect while minimizing side effects.

Minimal effective concentrations of Cl_2MDP probably are around 11.5 mg/kg/day (99) and for APD around 7.5 mg/kg/day (100).

5) Long term remissions - All of the diphosphonates thus far studied appear to be capable of causing long term remissions. There is much data available for EHDP treatment. Treatment with EHDP for as little as one month can lead to continued suppression of biochemical disease and to clinical improvement for at least one year after stopping treatment (95). Longer term treatment can lead to continued suppression of biochemical disease for up to two years (84). The length of remission after stopping EHDP may vary somewhat between patients but is generally considerable. About one-half of Khairi and coworkers' patients remained in clinical remission two years after stopping therapy (84). These authors also noted that if improvement was not experienced within six months of initiating treatment improvement should not be expected with further treatment. When patients experience relapse, it is most often both a clinical and biochemical relapse (52%), less often a clinical relapse without biochemical relapse (26%), and least often biochemical relapse alone (21%) (84).

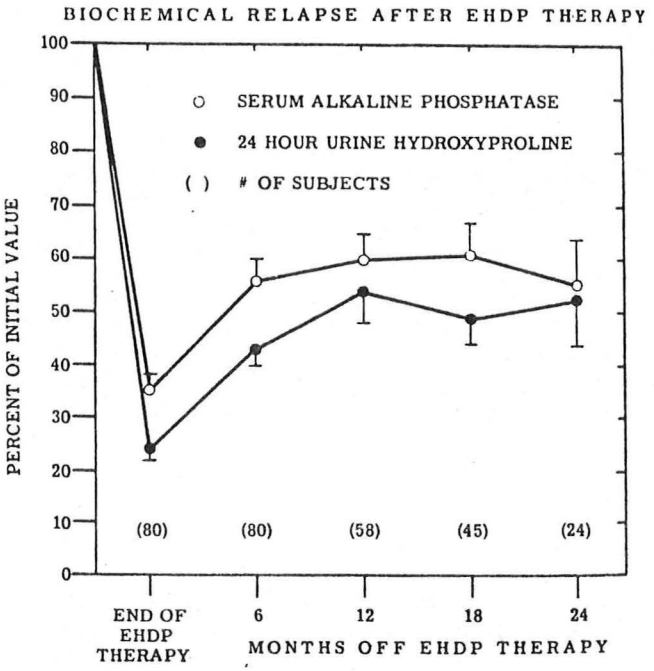


Figure 3. Changes in serum alkaline phosphatase and urinary hydroxyproline expressed as percent of initial value (mean ± SEM) at the end of sodium etidronate (EHDP) therapy and 6, 12, 18, and 24 months after withdrawal of the drug.

From: Khairi, M.R.A., Altman, R.D., DeRosa, G.P., et al. (1977) Sodium Etidronate in the Treatment of Paget's Disease of Bone, A Study of Long Term Results. Ann. Intern. Med. 87:656 (Reproduced with Permission)

Sufficient experience exists using Cl_2MDP to indicate that similar remissions occur with this agent. Although there are not yet published reports, it appears likely that ADP will also induce such long term remissions.

The long term remissions seen with diphosphonates really are not so surprising. Although only a small proportion of ingested oral diphosphonate is absorbed (1%-10%), almost all of the absorbed drug ends up localized to bone where it is bound very tightly (103). It would be expected that the bone concentration of drug and hence the inhibition of bone resorption would dissipate only very slowly. The persistence of drug in bone probably explains the generally long biochemical remissions seen with diphosphonate treatment.

Combination Therapy Using Both Calcitonin and Diphosphonates

Under certain circumstances it may seem reasonable to employ both diphosphonates and calcitonin in the same patient at the same time. There is some evidence that calcitonin can counter the ill effects of EHDP on bone mineralization (86), and/or that combined therapy may lead to better responses (104-107). At the most recent Endocrine Society meeting, neither Drs. J.A. Kanis nor T.J. Martin felt there was any benefit to combined therapy. Certain patients fail diphosphonates and respond to calcitonin and vice versa while a few patients may be resistant to either therapy. Both treatments together rarely accomplish more than a maximally efficacious dose of either. Combined therapy tends to produce the prolonged remissions characteristic of diphosphonate therapy (107).

TABLE 1. TEMPORAL RELATIONSHIP BETWEEN THE SCINTIGRAPHIC AND BIOCHEMICAL EVIDENCE OF RECURRENCE OF PAGET'S DISEASE

Scintigraphic activity	Biochemical parameters	Patient identification	Rise in scintigraphic activity after x months*	Rise in biochemical activity after x months†
Increasing	rise			
(21 patients)	(17 patients)	10	12	19
		43	14	22
		4	18	25
		25	18	25
		12	18	26
		23	18	38
		17	24	18
		18	24	18
		5	25	24
		61	25	26
		6	26	30
		71	27	27
		28	27	29
		20	29	26
		3	33	27
		84	43	36
		37	48	36
	no rise	1	23	—
	(2 patients)	7	29	—
	indeterminate	14	28	?
		27	26	?
No increase	rise	11	—	26
(19 patients)	(4 patients)	13	—	21
		15	?	28
		21	—	15
	no rise	2, 8, 9, 16,	—	—
	(15 patients)	19, 22, 24, 26,		
		29, 30, 52, 59,		
		74, 78, 88.		

* When scintigraphic deterioration occurred with respect to the initiation of therapy.

† Time of the earliest biochemical change (alkaline phosphatase or hydroxyproline) with respect to the start of treatment.

From: Vellenga, C.J.L.R., Pauwels, E.K.J., Bijvoet, Q.L.M., and Frilink, N.B. (1981) Scintigraphic Aspects of the Recurrence of Treated Paget's Disease of Bone. J. Nuclear Med. 22:510 (Reproduced with Permission)

Initial and Follow-up Evaluations of Patients with Paget's Disease

Before discussing specific indications for treatment, it is worthwhile to at least briefly discuss what testing should be done in the initial evaluation of Paget's disease and how disease activity should be followed. I started this discussion with three relatively typical case presentations for Paget's disease. It is likely that in the course of discovering any individual patient's disease, most useful information will already be obtained. At the time of initial evaluation alkaline phosphatase and acid phosphatase values should be checked. Urinary hydroxyproline values obtained while on a gelatin-free diet may be required if alkaline phosphatase values are only minimally elevated or normal.

An initial bone scan is useful in determining the extent of disease and in finding asymptomatic involvement. Radiographs of involved weight bearing bones are required to discover critical lytic disease. Since the placebo effect of treatment is so prominent in Paget's disease, it is essential to follow some biochemical parameter. The biochemical indicators of disease activity are all essentially equivalent. I generally follow serum alkaline phosphatase values since these values are inexpensive, easy to obtain from the patient, and readily available in most laboratories. Urine hydroxyproline or subfractions of hydroxyproline require 24-hour urine collections that are difficult for the patient to obtain. Bone GLA protein determinations are not readily available in most centers. There is no good reason to follow bone scans; you get the same information from a serum alkaline phosphatase at less cost and inconvenience. If lytic disease is present in weight bearing bones, it is probably advisable to follow plain films and document healing.

Evaluation of Patients with Paget's Disease

Initial Evaluation

biochemical tests	- alkaline phosphatase
	- acid phosphatase
	- hydroxyproline
radiographic tests	- bone scan
	- plain films of weight bearing bones

Follow-up Evaluation

biochemical tests	- alkaline phosphatase
radiographic tests	- plain films of lytic disease

Treatment Recommendations - Indications for Treatment and Efficacy of Treatment for Specific Complications

Treatment recommendations should be formulated by comparing the risk of the untreated disease with the efficacy, safety, cost, and convenience of therapy. Paget's disease generally has a very benign course and really does not merit any treatment. Although it is clear that treatment usually can significantly alter the biochemical parameters of disease activity, it is not nearly so clear that equivalent clinical benefit results. There are probably six defensible indications for treating Paget's disease. Treatment is indicated for the rather rare group of patients with: 1) symptomatic bone pain, 2) congestive heart failure, 3) neurologic complications, 4) immobilization hypercalcemia, 5) impending orthopedic surgery, and 6) very active disease in a young patients. Choice of therapy differs depending on the specific indications for therapy and are probably best considered as part of the discussion of specific treatment indications.

Indications for Treatment of Paget's Disease

- bone pain
- congestive heart failure
- neurological complications
- immobilization hypercalcemia
- impending orthopedic surgery
- very active disease in a young patient

Bone pain - Bone pain is the most common indication for treatment. In considering this indication, it is important to remember that the patient's pains may not be directly related to Paget's disease per se and that there is a powerful placebo effect of treating Paget's disease (about one-third of the patients get better without specific treatment). It is reasonable to take a very skeptical view of treatment and suspend treatment if a clear-cut biochemical remission is not obtained or if no clinical benefit occurs with a biochemical remission. Ideally, the patient will have pain at some site that is anatomically separated from joints so that a clinical remission can be better judged. For example, if the patient has involvement of the tibia with Paget's disease, he may have pain distant from any joint and local heat over the affected bone. It becomes relatively simple to judge a clinical remission in such patients. If, on the other hand, complaints center on back pain or pain within a joint, it may be very difficult to demonstrate a clinical benefit of therapy directed to the Paget's disease. It may be reasonable in many patients with joint-related complaints to start therapy with a nonsteroidal anti-inflammatory agent. If this therapy is quite effective in relieving pain, it may be unnecessary to pursue specific therapy of the Paget's disease.

Specific therapy may take one of several forms. My preference for initial therapy is a short course of high dose EHDP therapy. At the present time, this consists of EHDP 20 mg/kg/day by mouth for one month. Such treatment is favored as initial treatment because it has minimal toxicity, is quite inexpensive and easy to administer, and about as efficacious as any other treatment. If a clear-cut clinical and biochemical result occurs, the patient can be followed without any other treatment until relapse occurs, sometimes for as long as two years. If a significant biochemical response is not seen, lower dose EHDP may be employed for up to six months (5 mg/kg/day). If a biochemical response does not happen by six months, a response is not going to occur, and therapy with calcitonin should be attempted. A reasonable starting dose of calcitonin is 100 M.R.C.U. SQ three times per week. Lytic disease involving a weight bearing bone should probably not be treated with EHDP at all but with calcitonin at doses of 100 M.R.C.U. SQ each day. The expense of calcitonin treatment can be staggering, so it is important to document healing of lytic disease as soon as possible. If lytic disease heals, it is reasonable to stop the calcitonin and see if a prolonged biochemical and/or clinical remission will occur. If prolonged remission does not occur, then EHDP therapy can be initiated in all patients that are not diphosphonate resistant. Diphosphonate resistance is probably related to poor absorption of the drug and can probably be circumvented with the soon to be released IV diphosphonate preparations (102,103). At least under present protocols IV diphosphonate therapy requires about one week of continuous infusion and thus is not a first choice therapy for patients presenting with bone pain.

Congestive heart failure - Patients with Paget's disease typically have increased blood flow to the skin overlying affected bones and to the bones themselves (11-13). Congestive heart failure is always noted as a possible complication of this disease (1). This complication is very rare (1,2) and probably always is a combination of a high output state superimposed on an otherwise diseased heart. If a patient has extensive, active Paget's disease and heart failure that proves difficult to manage by conventional treatments, treatment of the Paget's disease is probably indicated since cardiac output can be decreased by such treatment (48). If the patient has disease extensive enough to significantly contribute to heart failure they probably also have other indications for treatment such as bone pain. Since the contribution of the Paget's disease to the heart failure is likely small, it is reasonable to treat these patients in the same manner as patients presenting with the primary complaint of bone pain. It would seem unlikely that acute suppression of Paget's disease with calcitonin

or IV diphosphonate is ever indicated. Emergency treatment of the heart failure should concentrate on the primary underlying heart disease.

Neurological complications - Neurological complications of Paget's disease may be devastating and at least some complications are treatable. Cranial nerve palsies generally do not improve with specific treatment of Paget's disease while symptoms referable to brainstem or spinal cord have a good chance of responding. Dysfunction of the brainstem or spinal cord can be caused by bony changes causing compression, from extramedullary hematopoiesis, or from vascular steal syndromes. Douglas and coworkers reviewed eight patients of their own and nineteen additional cases reported in the literature and concluded that about 90% of patients with spinal cord compression can improve with treatment (7). They were particularly impressed with the speed some patients recovered (less than two weeks in some cases) and suggested that the spinal cord syndrome could be explained by vascular steal (7). A report of a patient recovering within two days of intravenous EHDP therapy would be consistent with this view (108). At least one case of oropharyngeal dysphagia has improved on calcitonin treatment (10). Spinal or brainstem compression should be treated as an emergency. Treatment should aim to achieve maximal disease suppression in the shortest possible time. In the United States at the present time, the best way to accomplish prompt suppression is with calcitonin. Calcitonin given at doses of 100 M.R.C.U. SQ daily or twice daily will maximize treatment response. When intravenous EHDP becomes available, it should be used at 4.3 mg/kg/day given as a 3-4 hour infusion each day for seven days. After treatment has been initiated with calcitonin it is also reasonable to start oral diphosphonates as well. If there is no improvement with calcitonin and diphosphonate therapy and especially if there is radiographic evidence of an extradural mass, the possibility of extramedullary hematopoiesis should be considered. In one published case this complication caused myelopathy but responded dramatically to mithramycin (1.5 mg/day over eight hours for ten days) (8). The mithramycin was probably a good choice since it had effects on the Paget's disease as well as the extramedullary bone marrow. Oral EHDP has been reported to successfully reverse spinal compression (7) but should probably only be used with calcitonin since the onset of action is slow. When intravenous EHDP becomes available, it can be used as initial therapy in the dose and duration noted above. This treatment has resulted in the most dramatic relief of a neurological complication encountered thus far (108).

Table I. Review of other reported cases of medical treatment for spinal cord lesions in Paget's disease

Author	Number of patients	Treatment	Dose per day	Previous laminectomy	Recurrence after laminectomy	Result of medical treatment	Follow-up from start of treatment *(months)*
Alexandre *et al.* 1979	4	EHDP	5mg/kg	Yes	Yes	Complete	15
		EHDP	5mg/kg	No	—	Complete	12
		PCT SCT EHDP	NS NS 20mg/kg	No	—	Almost complete	42
		PCT EHDP Cl$_2$MDP	NS 10mg/kg 20mg/kg	Yes	Yes	Complete	15
Chen *et al.* 1979	6	SCT	100u	Yes (×4)	Yes	Almost complete	36
		PCT	200u	Yes	Yes	Complete	39
		PCT/SCT	50–200u	NS	—	Moderate improvement	NS
		PCT/SCT	50–200u	NS	—	No change	NS
		PCT/SCT	50–200u	NS	—	No change	NS
		PCT/SCT	50–200u	NS	—	No change	NS
Herzberg and Bayliss 1980	1	PCT	100u	No	—	Complete	12
Melick, Ebeling and Hjorth 1976	1	PCT	80–320u	No	—	Complete but relapsed	20
Nicolle *et al.* 1977	1	PCT	160–320u	Yes	Yes	Complete	51
Ravichandron 1979	1	SCT	100u	Yes	Yes (became completely paralysed)	Complete	20
Schumacher *et al.* 1977	2	SCT	200μg	Yes	No	Almost complete	12
		SCT	160u	Yes (×3)	No	Complete	24
Shai, Baker and Wallach 1971	2	PCT	200u	No	—	Almost complete	NS
		PCT	200u	No	—	Almost complete	NS
Walpin and Singer 1979	1	SCT	50u	No	—	Almost complete	22

EHDP = sodium etidronate, Cl$_2$MDP = dichloromethylene diphosphonate or clodronate disodium, SCT = salmon calcitonin, PCT = porcine calcitonin, NS = not stated.

From: Douglas, D.L., Duckworth, T., Kanis, J.A., et al. (1981) Spinal Cord Dysfunction in Paget's Disease of Bone. J. Bone and Joint Surg. 63:495 (Reproduced with Permission)

Immobilization hypercalcemia - Patients with Paget's disease frequently develop hypercalcuria when immobilized and occassionally may even develop frank hypercalcemia. Usually the hypercalcemia will not be severe, but if it is, it can be reasonably managed with calcitonin, 100 M.R.C.U. SQ each day for several days and then 100 M.R.C.U. SQ three times per week. Returning the patient to full

ambulatory status will usually cure the hypercalcemia in any case. If the patient cannot become ambulatory again (i.e. stroke), it may be more economical to treat with EHDP. If the serum calcium is very elevated and resistant to treatment, it is essential to think of and rule out other causes of hypercalcemia (58).

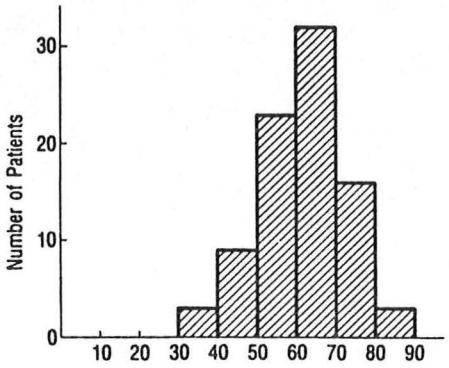
Impending orthopedic surgery - If orthopedic surgery is planned for a patient with Paget's disease, preoperative treatment of bone disease is advisable. Treatment is aimed at reducing the vascularity of the bone (13) and enhancing healing (58). Treatment should employ calcitonin 100 M.R.C.U. SQ each day for three months before surgery and six to twelve months after surgery. Since all diphoshonates thus far characterized cause bone cell hypoplasia, they are contraindicated in such patients.

Active disease in a young patient - This last indication for treatment is the most arguable. Biochemically and radiographically very active disease in an otherwise asymptomatic patient is rare but is occassionally encountered. These patients are probably at great risk for eventually developing rheumatic, orthopedic, or neurological complications of Paget's disease. In patients younger than sixty such active disease is especially worrisome since they have a long time to accumulate complications of their disease. Ideally, such patients would be treated with therapy that has no significant complications even when employed for many years. Because there are theoretical reasons to be concerned about very long term diphosphonate use and because few patients have been treated for long periods with diphosphonates, I would favor three times per week calcitonin injections (100 M.R.C.U.) over diphosphonate therapy. If a biochemical remission is induced and maintained and if the patient can afford this type of treatment, it probably should be continued. If the calcitonin treatment is ineffective or "escape" occurs, treatment should be switched to intermittent diphosphonate therapy. This should be done with EHDP, 20 mg/kg/day orally for one month. The patient can then be left unmedicated until definite biochemical relapse occurrs. Following this approach it should be possible for the patient to spend most of the time without medicines. Hopefully this approach will minimize bone marrow exposure to diphosphonate.

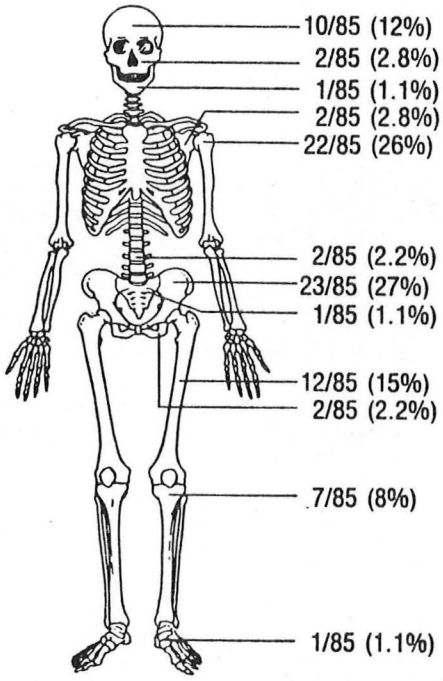
Bone Tumors in Paget's Disease

Three types of bone tumors are reported to occur in patients with Paget's disease. Most common are osteogenic sarcomas (1,2,4). These tumors are highly malignant and despite aggressive treatment are almost always fatal. In the series of 85 patients described by Smith and coworkers, only three patients survived more than five years despite aggressive use of amputation, radiation, and chemotherapy. The sarcomas were not heralded by a dramatic increase in the serum alkaline phosphatase nor was there a characteristic bone scan appearance (4). Although it has been emphasized that such tumors take up diphosphonate bone scan tracers, Smith and coworkers as well as others (109) have seen negative bone scans in some patients. One interesting feature of the sarcomas is that they tend to be most frequent in parts of the skeleton least frequently affected by Paget's disease. Much less frequent than osteosarcomas are benign giant cell tumors or giant cell reparative granulomas (110). These tumors may in fact be the same, usually are found in the facial bones, and are easily treated with radiation.

Figure 1



Incidence by age (in decades) of the 85 patients.



Skeletal distribution in 85 cases of Paget sarcoma.

From: Smith, J., Botet, J.F., and Yeh, S.D.J. (1984) Bone Sarcomas in Paget's Disease: A Study of 85 Patients. Radiology 152:583 (Reproduced with Permission)

Conclusions

Paget's disease is a fairly common disease of bone. Older asymptomatic patients should not be treated. Such patients would not significantly benefit from even highly effective specific therapy. A much smaller group of patients has symptomatic disease or one of the rare orthopedic, neurological or cardiovascular complications of their disease. Such patients merit treatment. In this highly selected group of patients treatment can be shown to be effective in reversing several specific complications.

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