

Regular Review

Paget's disease of bone

D J HOSKING

In Paget's disease a greatly accelerated rate of remodelling is combined with the development of structurally abnormal bone. The last decade has seen a revival of interest in this common skeletal disorder as a result of two developments. Mithramycin, calcitonin, and the diphosphonates have opened up the possibility of controlling bone turnover effectively, and this has coincided with growing interest in the complexities of the remodelling of bone at a cellular level. Research has been stimulated both by the requirements for information about cellular mechanisms and by the prospect of therapeutic advance.

Sir James Paget's original description of the disease over a century ago under the title "osteitis deformans" incorporated both his own aetiological preference and his view of its commonest manifestation.¹ Deformity is now recognised to be less common than bone pain as a symptom, but inflammation is once more returning to favour as the underlying disease process.

Pathogenesis

Paget's disease seems likely to be primarily a disorder of osteoclasts,² with the other cellular mechanisms a secondary phenomenon mediated through the well-recognised, but poorly understood, link between bone resorption and formation.³ The osteoblasts are more active than normal in producing bone matrix, much of which may be woven rather than lamellar, but neither they nor the osteocytes show any morphological abnormalities.⁴ In contrast, the osteoclasts show several characteristic changes, some of which are specific to Paget's disease.⁴⁻⁵ These cells are very active metabolically as shown by the presence of numerous mitochondria, an abundant endoplasmic reticulum, and a well-developed Golgi apparatus. The cytoplasmic membrane is usually appreciably indented, particularly in the region of the ruffled border opposed to bone; and this appearance, together with the presence of collagen fragments, apatite crystals, and occasional whole bone particles within the cytoplasm suggests that the cells' resorbing activity and surface mobility are greatly increased.

A unique feature of osteoclasts in Paget's disease is the presence of spherical or ovoid cytoplasmic and nuclear inclusion bodies, which have a paracrystalline structure composed of microtubules about 15 nm in cross-section.⁴⁻⁶ The intranuclear and intracytoplasmic inclusion bodies seem similar; some may be in physical continuity across the nuclear membrane. The similarity between these inclusion bodies and the nucleocapsids of the paramyxovirus of the measles group found in subacute sclerosing panencephalitis⁷ raises the possibility that Paget's disease, too, might be due to a slow virus infection.

There is no conclusive proof that Paget's disease is due to a virus, but the data go some way to satisfying Koch's postulates. Firstly, inclusion bodies are found almost invariably in osteoclasts from Paget's disease, though they are not present in every nucleus of every cell; they are absent in other cell lines such as osteoblasts and marrow cells. They have never been seen in osteoclasts from other high turnover diseases such as hyperparathyroidism, though they have been reported in osteoclasts from a few giant cell tumours of bone.⁸ Secondly, when bone cells from Paget's disease have been maintained in tissue culture they retain their inclusion bodies through several passages.⁹ The third and critical postulate, the ability to reproduce the disease in susceptible animals, has been difficult because of the lack of a model for Paget's disease. Further supportive evidence has therefore been indirect. Immunofluorescence studies using high titre measles antibody or serum from a patient with subacute sclerosing panencephalitis have shown that osteoclasts from Paget's disease contain antigenic material belonging to or cross-reacting with antibodies against this viral group.⁵ Though the presence of measles virus has not been an invariable finding, similar studies have shown immunofluorescence to other RNA viruses bearing similarities to respiratory syncytial virus.⁹

Many of the general features of a slow virus infection—long latent period, absence of acute inflammation or fever, localisation in a single organ—would be consistent with the clinical course of Paget's disease. Furthermore, an early cytopathogenic effect of measles virus is the development of giant multinucleated cells by the fusion of infected with non-infected cells. Possibly a similar mechanism might lead to the development of the typical multinucleated osteoclasts of Paget's disease.⁴ Certainly infection seems the leading aetiological contender at present.

Clinical features and indications for treatment

Most patients with Paget's disease have no symptoms, and since the disorder is usually associated with little morbidity or mortality treatment is not required. Bone pain unresponsive to simple analgesics is the usual indication for active intervention; much less common symptoms are due to syndromes of neurological compression, to immobilisation hypercalcaemia and hypercalcaemia, and perhaps high output cardiac failure. Patients being prepared for orthopaedic surgery may also need treatment.² There is no evidence that treatment improves or prevents the development of deformity, long bone fractures, or the exceedingly rare complication of sarcomatous change.

Evaluation of the effects of treatment is usually subjective and attended by a high placebo response.¹⁰ For example, pain may arise either from an area of Paget's disease within a bone

or from osteoarthritic change in adjacent joints. Clinical trials must therefore take both variables into account as well as allowing for a placebo effect; few such studies have been reported.^{10 11} Because of these difficulties, most studies have relied heavily upon changes in urinary hydroxyproline excretion and serum alkaline phosphatase activity as an indication of the osteoclastic and osteoblastic responses to treatment. The problem of assessing benefit is becoming more pressing with the recent development of more effective forms of treatment which offer the potential for long-term control.^{12 16} Current drugs may tempt the clinician to treat younger patients with milder symptoms in the expectation of preventing extension of the disease and the development of long-term complications. At present there is no evidence to show that such an approach is either safe or desirable.

Treatment

Calcitonin has been available for just over a decade. It will improve many of the clinical features of the disease but does not effect a cure. For the reasons outlined above it is not surprising that the proportion of patients reported as responding in different series has varied from 30% to 80%.¹⁷⁻¹⁹ Porcine, salmon, and human calcitonins probably have few qualitative differences but the greater potency on a weight-for-weight basis and its more prolonged action makes salmon calcitonin the preparation of choice.

Individuals vary considerably in their sensitivity to calcitonin, but maximal reductions in turnover are usually achieved with doses of 350 to 700 Medical Research Council units a week. Less than 150 units provides a submaximal degree of control. In most cases alkaline phosphatase activity and hydroxyproline excretion will be reduced by about half with the nadir reached in the first six months of treatment.¹⁷⁻²⁰ Patients with more than a twofold to threefold increase in bone turnover will therefore be left with residual activity which cannot be reduced by an increase in the dose or duration of treatment.^{17 21} Though the histological evidence shows that bone remodelling shifts to a more lamellar pattern during treatment with calcitonin,^{22 23} the abnormalities are only partially corrected. Once calcitonin is withdrawn bone turnover usually increases towards pretreatment levels,^{21 24} but symptoms may remain controlled, perhaps as a consequence of the bone remodelling produced by calcitonin. Clearly the hormone has a transient suppressive rather than curative effect on bone.

Porcine calcitonin and salmon calcitonin are antigenic in man because of the difference between their amino-acid sequence and that of the human hormone. Nevertheless, while antibodies develop in one-third to two-thirds of patients given exogenous calcitonins,^{17 19 20 25 26} there is no evidence that the general failure of the hormone to control bone turnover has an immune basis. True resistance is unusual²⁰ but may become more common with prolonged treatment, because antibody titres usually, but not invariably, increase with time. The presence of resistance can be confirmed by showing that the control of bone turnover is restored by the use of a calcitonin to which antibodies are absent.^{20 25 26} If treatment needs to be continued in a patient with resistant disease (and there may be few indications for this) then use of the non-antigenic human hormone is preferable to that of an exogenous calcitonin. Unfortunately human calcitonin is not commercially available and supplies are limited.

Some patients without antibodies or treated with human calcitonin show a pattern of change of bone turnover similar to

that seen in patients with resistant disease.^{20 27} This puzzling phenomenon and the failure of calcitonin to return bone turnover to normal raise the whole question of the mechanism of the cellular action of calcitonin—does it act primarily on osteoclast activity or on the activation of new bone remodelling units? Until these questions are answered the use of calcitonin will be restricted to providing relatively short-term symptomatic relief from a condition whose underlying mechanism remains unchecked.

The introduction of the diphosphonates into clinical medicine has been one of the most interesting developments in the last decade.²⁸ Most of the studies in Paget's disease have used disodium etidronate: disodium ethane 1-hydroxy-1-diphosphonate,^{10 29-33} a synthetic analogue of pyrophosphate in which the P-O-P bond is replaced by P-C-P, making the diphosphonates more resistant to hydrolysis. These compounds have a high affinity for calcium phosphate crystals, so that they are rapidly cleared from the blood and their biological effects are largely confined to bone. The highest concentrations are to be expected at sites of mineralisation and resorption, but the diphosphonates may also enter osteoclasts absorbed to bone fragments during resorption. The diphosphonates are powerful inhibitors of crystal formation and dissolution, but inhibition of bone resorption is certainly more complex and may depend on intracellular mechanisms.²⁸

Disodium etidronate is given by mouth, though less than 10% of the dose is absorbed; that fraction not taken up by bone is excreted unchanged in the urine. The drug is well tolerated apart from occasional mild abdominal symptoms which do not appear dose dependent. Pain is relieved in about 60% of patients; relief shows a roughly linear relationship to administered dose, and is usually maximal within six months, though it may persist for several months once the drug is withdrawn.²⁹⁻³¹

The greatest effect on bone turnover is usually achieved within the first six months of treatment, by which time a reduction of about half will have been achieved.^{10 31 33} Though higher doses of disodium etidronate produced a slightly better fall in hydroxyproline excretion the effect on alkaline phosphatase activity varies little within the range 5-20 mg/kg (400-1600 mg/day).^{10 29-32} As with calcitonin the initial disease activity is the major factor determining whether bone turnover will return to normal with treatment. With moderate disease activity (roughly threefold increase in turnover) normal values are often achieved using 5 mg/kg for six months, and this response may persist for as long as two to three years once disodium etidronate is withdrawn.^{10 30-32} Patients with more active disease show a less complete response and a greater tendency to relapse once treatment is withdrawn,^{10 30 32} but they seem to respond better to disodium etidronate than to calcitonin. Biochemical relapse can be prevented by sequential use of disodium etidronate with either 5 mg/kg given for six months of every year or 20 mg/kg given for one month out of every four.³² Since retreatment on clinical relapse seems just as effective as the initial course of disodium etidronate,^{10 31 33} the benefit to be obtained from drug-induced suppression—even though it seems free from important side effects—is uncertain and this approach remains experimental.³²

At a cellular level disodium etidronate causes a dose-dependent suppression of the numbers of osteoclasts and resorbing activity. The rate of calcification is reduced to within the normal range by 5 mg/kg but at higher doses osteoid thickness increases significantly.^{10 31} These changes are most noticeable in the areas affected by Paget's disease

but are also seen to a less extent in bone elsewhere. Defective mineralisation is the main problem associated with treatment with high doses of disodium etidronate and may be accompanied by a recrudescence of bone pain or non-traumatic fractures.^{10 30 33} Since these histological and clinical problems are not seen with 5 mg/kg, at which dose the degree of suppression of bone turnover is almost optimal, there seems little indication for the use of higher doses except for short periods of a few weeks.³²

A combination of calcitonin (50 to 100 units daily) with disodium etidronate in doses low enough to avoid the development of complications may have substantial advantages over the use of either drug alone. Preliminary data suggest that most patients achieve normal or near normal bone turnover irrespective of the initial disease activity, with alkaline phosphatase activity and hydroxyproline excretion declining with a half time of about six weeks.^{12 13} Defective mineralisation has not been seen at this dose of disodium etidronate (7.5 mg/kg) even though the excessive osteoclastic activity was controlled. Provided that the histological appearance of the bone is monitored regularly there seems no reason why treatment should not continue so long as bone turnover continues to decline. The same studies also suggested that three patients out of four stay in remission for at least six months after stopping treatment, and in some this may last up to two years. Nevertheless, more data are required—particularly relating to the degree of control and maintenance of remission in very active Paget's disease—before this combination can be established as a standard form of treatment.

The same reservations probably apply to two of the second

generation diphosphonates, 3-amino-1-hydroxypropylidene 1-1-bisphosphonic acid^{15 16} and dichloromethylene diphosphonate,^{14 34} both of which appear extremely effective in Paget's disease. These compounds seem to have a much wider margin between the dose that inhibits bone resorption and that affecting growth or mineralisation of bone. In preliminary studies both compounds seem able to reduce bone turnover to normal or near normal within six months in patients with moderately severe disease. An interesting phenomenon with both drugs is the very rapid inhibition of bone resorption (normal levels of hydroxyproline excretion within the first week of treatment with 3-amino-1-hydroxypropylidene 1-1-bisphosphonic acid at a dose of 9 mg/kg) compared with the much slower reduction in bone formation. This suggests very strongly that these compounds primarily affect bone resorption and that the effect on bone formation is a secondary response. Defective mineralisation does not occur with either of these agents at current doses.

These preliminary studies hold great promise, and if the new diphosphonates are shown to be capable of restoring normal turnover irrespective of the initial disease activity without the development of important side effects then they are a real advance. Potency seems associated with a persistence of control once the drug is withdrawn, and since a cure for Paget's disease is likely to elude us until the cause is known this is another real advantage.

D J HOSKING

Senior lecturer,
Department of Medicine,
University Hospital,
Nottingham NG7 2UH

- 1 Paget J. On a form of chronic inflammation of bones (osteitis deformans). *Medico-Chirurgical Transactions* 1877;**60**:37-64.
- 2 Singer FR, Schiller AL, Pyle EB, Krane SM. Paget's disease of bone. In: Avioli LV, Krane SM, eds. *Metabolic bone disease*. Vol 2. New York: Academic Press, 1978:489-575.
- 3 Parfitt AM. The actions of parathyroid hormone on bone: relation to bone remodelling and turnover, calcium homeostasis and metabolic bone disease. I. Mechanisms of calcium transfer between blood and bone and their cellular basis: morphological and kinetic approaches to bone turnover. *Metabolism* 1976;**25**:809-44.
- 4 Rebel A, Basle M, Pouplard A, Malkani K, Filmon R, Lepatezour A. Bone tissue in Paget's disease of bone. Ultrastructure and immunocytochemistry. *Arthritis Rheum* 1980;**23**:1104-14.
- 5 Rebel A, Malkani K, Basle M, Bregon CL. Osteoclast ultrastructure in Paget's disease. *Calcified Tissue Research* 1976;**20**:187-99.
- 6 Mills BG, Singer FR. Nuclear inclusions in Paget's disease of bone. *Science* 1976;**194**:201-2.
- 7 Raine CS, Feldman LA, Sheppard RD, Bornstein MB, Barbosa LH. Subacute sclerosing panencephalitis virus. Observations on a neuroadapted and non-neuroadapted strain in organotypic central nervous system cultures. *Lab Invest* 1974;**31**:42-53.
- 8 Welsh RA, Meyer AT. Nuclear fragmentations and associated fibrils in giant cell tumor of bone. *Lab Invest* 1974;**23**:1115-20.
- 9 Mills BG, Singer FR, Weiner LP, Holst PA. Cell cultures from bone affected by Paget's disease. *Arthritis Rheum* 1980;**23**:1115-20.
- 10 Khairi MRA, Altman RD, DeRosa GP, Zimmerman J, Schenk RK, Johnston CC. Sodium etidronate in the treatment of Paget's disease of bone. A study of long-term results. *Ann Intern Med* 1977;**87**:656-63.
- 11 Bouvet J-P. The treatment of Paget's disease using salmon thyrocalcitonin: a co-operative double-blind trial. *Nouv Presse Med* 1977;**6**:1447-50.
- 12 Hosking DJ, Bijvoet OLM, Van Aken J, Will EJ. Paget's bone disease treated with diphosphonate and calcitonin. *Lancet* 1976;**ii**:615-7.
- 13 Bijvoet OLM, Hosking DJ, Frijlink WB, Velde JT, Vellenga CJLR. Treatment of Paget's disease with combined calcitonin and diphosphonate (EHDP). *Metabolic Bone Disease and Related Research* 1978;**1**:251-61.
- 14 Meunier PJ, Chapuy MC, Alexandre C, et al. Effects of disodium dichloromethylene diphosphonate on Paget's disease of bone. *Lancet* 1979;**iii**:489-92.
- 15 Frijlink WB, Bijvoet OLM, Te Velde J, Heynen G. Treatment of Paget's disease with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). *Lancet* 1979;**ii**:799-803.
- 16 Bijvoet OLM, Frijlink WB, Jic K, et al. APD in Paget's disease of bone. Role of the mononuclear phagocyte system? *Arthritis Rheum* 1980;**23**:1193-204.
- 17 DeRose J, Singer FR, Avramides A, et al. Response of Paget's disease to porcine and salmon calcitonins. Effects of long-term treatment. *Am J Med* 1974;**56**:858-66.
- 18 Kanis JA, Horn DB, Scott RDM, Strong JA. Treatment of Paget's disease of bone with synthetic salmon calcitonin. *Br Med J* 1974;**iii**:727-31.
- 19 Martin TJ, Jerums G, Melick RA, Xipell JM, Arnott R. Clinical, biochemical and histological observations on the effect of porcine calcitonin in Paget's disease of bone. *Aust NZ J Med* 1977;**7**:36-43.
- 20 Singer FR, Fredericks RS, Minkin C. Salmon calcitonin therapy for Paget's disease of bone. The problem of acquired clinical resistance. *Arthritis Rheum* 1980;**23**:1148-54.
- 21 Evans IMA, Banks L, Doyle FH, et al. Paget's disease of bone—the effect of stopping long term human calcitonin and recommendations for future treatment. *Metabolic Bone Disease and Related Research* 1980;**2**:87-92.
- 22 Meunier P. Paget's disease of bone. Quantitative histology, histopathogenesis and therapeutic prospects. *Lyon Medical* 1975;**233**:839-53.
- 23 Rasmussen H, Bordier P. Primary disorders of bone cell function. In: Rasmussen H, Bordier P, eds. *Physiological and cellular basis of metabolic bone disease*. Baltimore: Williams and Wilkins, 1974:292-303.
- 24 Avramides A, Flores A, DeRose J, Wallach S. Paget's disease of the bone: observations after cessation of long-term synthetic salmon calcitonin treatment. *J Clin Endocrinol Metab* 1976;**42**:459-63.
- 25 Haddad JG Jr, Caldwell JG. Calcitonin resistance: clinical and immunologic studies in subjects with Paget's disease of bone treated with porcine and salmon calcitonin. *J Clin Invest* 1972;**51**:3133-41.
- 26 Singer FR, Aldred JP, Neer RM, Krane SM, Potts JT Jr, Bloch KJ. An evaluation of antibodies and clinical resistance to salmon calcitonin. *J Clin Invest* 1972;**51**:2331-8.
- 27 MacIntyre I, Evans IMA, Hobitz HHG, Joplin GF, Stevenson JC. Chemistry, physiology and therapeutic applications of calcitonin. *Arthritis Rheum* 1980;**23**:1139-47.
- 28 Fleisch H. Experimental basis for the clinical use of diphosphonates in Paget's disease of bone. *Arthritis Rheum* 1980;**23**:1162-71.
- 29 Khairi MRA, Johnston CC Jr, Altman RD, Wellman HN, Serafini AN, Sankey RR. Treatment of Paget's disease of bone (osteitis deformans). Results of a one-year study with sodium etidronate. *JAMA* 1974;**230**:562-7.
- 30 Canfield R, Rosner W, Skinner J, et al. Diphosphonate therapy of Paget's disease of bone. *J Clin Endocrinol Metab* 1977;**44**:96-106.
- 31 Johnston CC Jr, Khairi MRA, Meunier PJ. Use of etidronate (EHDP) in Paget's disease of bone. *Arthritis Rheum* 1980;**23**:1172-6.
- 32 Siris ES, Canfield RE, Jacobs TP, Baquiran DC. Long-term therapy of Paget's disease of bone with EHDP. *Arthritis Rheum* 1980;**23**:1177-84.
- 33 Finerman GAM, Gonick HC, Smith RK, Mayfield JM. Diphosphonate treatment of Paget's disease. *Clin Orthop* 1976;**120**:115-24.
- 34 Douglas DL, Duckworth T, Kanis JA, et al. Biochemical and clinical responses to dichloromethylene diphosphonate (Cl₂MDP) in Paget's disease of bone. *Arthritis Rheum* 1980;**23**:1185-92.