deficiency (PNH II) and one with complete deficiency (PNH III)[10] of GPI-linked proteins, have two clones made manifest by their different phenotype. In addition, since we have shown that two co-existing clones may have the same phenotype, even patients who have only PNH III cells may have two clones. Further analysis might reveal more than two PNH clones in the same patient.

Our data may have a bearing on the association between PNH and aplastic anaemia. In principle, this association might be explained by the PNH clone suppressing normal haemopoiesis—ie, PNH causes aplastic anaemia. The co-existence of two clones suggests instead that aplastic anaemia is the primary event that enables PNH clone(s) to flourish. We do not know the mechanisms of inhibition of normal haemopoiesis that is responsible for aplastic anaemia (with or without PNH). But the absence of GPI-linked proteins may enable the PNH cells to escape this inhibition. Thus, the somatic mutations in the *PIG-A* gene, which abolish or decrease the expression of GPI-anchored membrane proteins, allow successful maintenance of haemopoiesis; perhaps this is nature's gene therapy. Gene therapy can be expensive, and in patients with depressed haemopoiesis the price to pay is PNH.

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Long-term effects of intravenous pamidronate in fibrous dysplasia of bone

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Nine patients with symptomatic and severe fibrous dysplasia were treated with intravenous pamidronate (60 mg per day over 3 days every sixth month), and were followed up for 18–48 months. The major effect was decreased bone pain (complete remission in 12 of 14 sites). Radiological changes were seen in four patients, with thickening of cortices, refilling of osteolytic lesions, or both. The initial increased bone remodelling was reduced, as shown by decrease of raised serum alkaline phosphatase and urinary hydroxyproline. The treatment was well tolerated, but a 13-year-old patient showed widening of knee growth-plates which is consistent with a transient mineralisation defect.

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Fibrous dysplasia of bone is a rare congenital disease leading to osteolytic lesions. Initial manifestations occur during childhood (fragility fractures, bone pain, and bone deformity). Because of some analogy with Paget's disease of bone, in particular increased osteoclastic resorption at the interface between marrow fibrous invasion and bone, the use of antiresorptive compounds has been proposed. We aimed to evaluate the long-term effects of intravenous pamidronate in patients with fibrous dysplasia of bone.

Nine consecutive patients have been treated with pamidronate (4 male, 5 female; 13–59 years of age, mean 33). They have been followed up for between 18 and 48 months (mean 26) after the first course. Eight patients had a polyostotic form of fibrous dysplasia (McCune-Albright syndrome) and one had monostotic involvement of the right femur. All but one had already sustained one or more fractures. The diagnosis was confirmed histologically in six patients. For the other three, radiological findings were characteristic enough for diagnosis without histology.

Pamidronate 180 mg was given in continuous infusion over 72 h in normal saline or glucose solution. The treatment was repeated every sixth month in most cases. Patients were usually supplemented with calcium 500–1500 mg per day and vitamin D2 800–1200 IU per day.

All involved sites were radiographed at baseline and at each follow-up. Laboratory tests were done before treatment and at 3, 6, 12, and 18 months, and included serum calcium, phosphate, and alkaline phosphatase and urinary hydroxyproline and calcium by standard methods. Serum intact parathyroid hormone and calcifediol were also measured, and in five patients we studied at baseline more specific bone markers: serum osteocalcin and bone alkaline phosphatase, and urinary pyridinoline and deoxypyridinoline. Pain intensity was assessed at each painful site as severe, moderate, or nil.

Initial biochemical data were compared with control values from normal subjects by unpaired *t* test. The study data were analysed with two-way analysis of variance (ANOVA) and, if significant, with paired *t* test.

Before the first treatment, our nine patients had 14 painful sites (severe in 8 and moderate in 6) with, in three cases, "inflammatory" symptoms (increase of local heat and tenderness on pressure). Pamidronate decreased pain intensity in all cases. Pain completely disappeared in 12 sites (6 that had been graded severe and 6 that had been moderate), and in 2 sites pain decreased from severe to moderate. This led to rapid improvement with decrease of "inflammatory" symptoms. After each infusion of

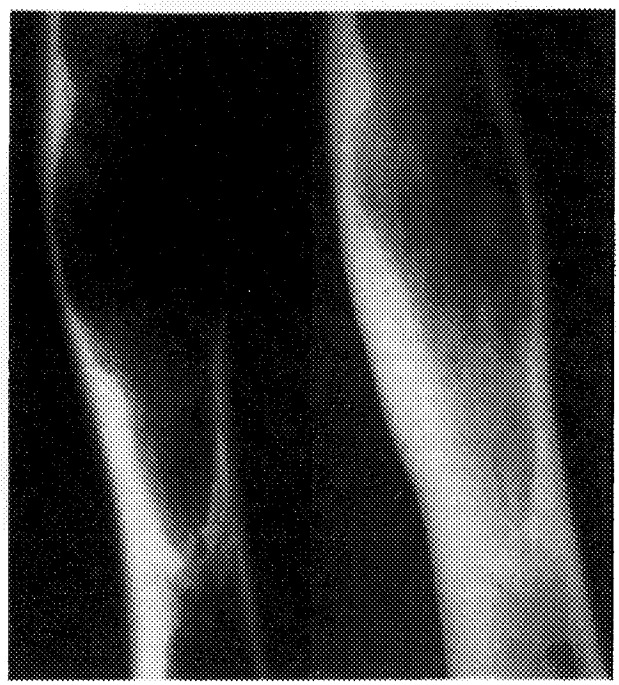

Figure: **Thickening of femoral cortex over 24 months**

pamidronate, residual pain intensity decreased and pain improvement continued. During the entire follow-up, representing 19·5 patient-years, no fracture occurred.

Four patients had radiological changes: progressive refilling of osteolytic areas and cortical thickening. Two showed progressive reduction in the size of a lytic lesion of the femur over 2 years. Another patient showed thickening of the femoral cortex with reduction of a lytic area (figure). In one case, a wide sub-trochanteric fissure progressively disappeared.

Mean serum calcium, phosphate, parathyroid hormone, and calcifediol D and urinary calcium were normal before treatment and did not change during follow-up. Serum alkaline phosphatase and osteocalcin, bone alkaline phosphatase, and urinary hydroxyproline, pyridinoline, and deoxypyridinoline were higher than normal values at baseline ($p<0·01$ or $<0·02$). Successive infusions of pamidronate decreased serum alkaline phosphatase and urinary hydroxyproline. Mean (SD) percentage decreases at 3, 6, 12, and 18 months were respectively: −26 (17) and −29 (19) (both $p<0·005$); −26 (10) ($p<0·001$) and −14 (39) (not significant); −24 (13) ($p<0·005$) and −19 (11) ($p<0·001$); and −24 (11) ($p<0·001$) and −19 (22) ($p<0·05$).

Side-effects were those usually described with intravenous pamidronate: transient fever (3), symptomatic hypocalcaemia (2), and transient diffuse bone pain (2). Our youngest patient (aged 13) who received three courses of pamidronate had unusual right-knee changes. The thickness of the growth-plate on the internal side of both the femur and tibia expanded over 18 months, which suggested a mineralisation defect similar to that in rickets. After 24 months these lesions had healed (radiography). A transiliac bone biopsy at 7 months after the last course of pamidronate in a bone affected by fibrous dysplasia revealed histomorphometric evidence of a mineralisation defect: cancellous osteoid volume and osteoid width were increased: 23·6% (normal 3·9 [2·3]%) and 22·8 μm (7·3 [0·4] μm), respectively.

The pathogenesis of fibrous dysplasia is poorly known and impairment of bone-forming mesenchyma is likely. In active disease, high bone-turnover is reflected by raised serum alkaline phosphatase and urinary hydroxyproline, and this encouraged some open trials with calcitonin[1-4] and etidronate.[5,6] But the two markers were not reduced, and there was no clinical or radiological change. Pamidronate potently inhibits bone resorption and, as with other bisphosphonates, has a prolonged effect on bone turnover.[7] We chose 180 mg, which is the dose for Paget's disease of bone resistant to etidronate.

The efficacy of pamidronate infusions to alleviate pain was most obvious in patients with pseudo-inflammatory signs of high bone-turnover. The biochemical changes we induced with pamidronate are consistent with reduced bone remodelling. More importantly, radiography showed reduced lytic areas and thickening of cortices in four cases, and no extension of pre-existing lesions was seen. So pamidronate may have increased bone strength in sites affected by fibrous dysplasia, and hence decreased fracture risk. The changes observed in a teenager on the knee growth-plates were caused by inhibition by pamidronate of mineralisation. Mineralisation defects have been reported in four pagetic patients treated with pamidronate.[8] Tiludronate at a high daily dose (40 mg/kg) for 12 months in baboons induced reversible changes of the growth plate, similar to the findings in our patient.[9]

Thus intravenous pamidronate led to clinical and radiological improvement in fibrous dysplasia via reduced bone remodelling. Further studies are warranted, especially in young patients in whom the disease is more symptomatic and the potential consequences of bisphosphonates on growth-plate mineralisation have to be taken into account.

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