were corrected in three days by intravenous perfusions of saline solutions, without nasal oxygen therapy or artificial ventilation. The treatment of metabolic alkalosis is based on the correction of hypovolaemia by perfusions of chloride-containing solutions, since hypochloraemia maintains metabolic alkalosis. The spontaneous ventilatory compensation of metabolic alkalosis in these patients suggests that the respiratory centre depression produced in severe alkalosis predominates over the stimulatory effects of hypercapnia and hypoxia. By recognition of such hypercapnia as a life-saving response unjustified artificial ventilation may be avoided.

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Paget's disease of bone

SIR,—Dr D J Hosking (21 November, p 1402), in his reply to our letter (17 October, p 1054), better emphasised the point we wanted to make than we did ourselves. Indeed, he stressed that at 20 mg/kg/24 h etidronate does induce specific adverse clinical and histological (as well as radiological[1]) changes, and a host of fractures.[1-3] These effects can be seen by the naked eye and subjectively, and as many patients deteriorate as improve.[3] The point we wanted to make was that to find out what happens at lower dosages, the cases must be evaluated more carefully and the osteolytic lesions must be prospectively studied by the most refined *x*-ray techniques. In Paget's disease these techniques cannot be replaced by any other method. Only *x*-ray examination can reveal what happens at the site of the osteolytic lesions where etidronate reaches its highest concentrations. At the lower dosages we admit that generalised osteomalacia does not occur in all cases, although it does in some,[4] and that only a minority of the patients had to interrupt therapy. It must be underlined that in no case did a uniformly positive focal bone balance occur, contrary to what was seen with calcitonin.

It is true, as Dr Hosking pointed out, that the average dose we used was 7·0 mg/kg/24 h of etidronate. It was, however, 6·2 mg/kg/24 h in our first study which resulted in similar conclusions.[5] Furthermore, it is impossible to administer exactly the "ideal" 5·0 mg/kg/24 h dose with non-breakable 200 mg tablets unless the patients weigh exactly 40 or 80 kg, which was not the case. The 5 mg/kg/24 h dose is the one which is desired but which is seldom achieved when it is actually calculated. Furthermore, negative changes have been observed with the 5 mg/kg/24 h dose as well. We emphasised the point that the degree of absorption (which is highly variable) is more crucial than the amount given and also the concentration achieved in those skeletal sites where activity is highest. This concentration, in turn, depends on the competition of other active skeletal sites for the bone-seeking drug. Finally, it is the end-product of all these factors that is of importance for pagetic lesions, and there is consequently no dosage at which osteolytic lesions are uniformly safe. We feel, therefore, that during etidronate therapy it is more important to follow the patient's fasting serum phosphate level, a reflection of the serum concentration of etidronate, than the alkaline phosphatase value.

Dr Hosking is correct when he says that our series is small, but it is intentionally so as we felt it unethical to continue to administer a drug which was not radiologically beneficial to any of our patients with osteolytic lesions, and was clinically detrimental in three patients out of nine. He is also correct in saying that our data have not yet been reproduced. In all cases where we had to withdraw the medication, however, striking radiological deterioration occurred. We quoted in our letter three authors who noticed subjective adverse effects during therapy, and have subsequently heard the same from several others. We assume that if *x*-ray films of these cases had been studied they would have shown the same focal negative bone balance. M L Smith, I Fogelman, B F Boyce, and I T Boyle from the University of Glasgow recently gave a presentation at a Bone and Tooth Society meeting in London entitled "Skeletal complications of Didronel therapy." In this series of 14 patients given 400 mg/24 h of etidronate orally for six months, three patients developed fissure fractures—two in grossly deformed pagetic tibiae, the third in the pubic ramus. Bone biopsy specimens from the iliac crest showed histological evidence of focal osteomalacia in some patients following therapy. These lesions were not confined to those patients who developed fractures. On the basis of these data and others we do not feel that our experience is unique.

Finally, Dr Hosking misread us when he states that in our opinion etidronate therapy should be completely dismissed in Paget's disease. We consider it advisable not to use it in *osteolytic* Paget's disease. Russell *et al*[6] advise treatment of "patients with severe active osteolytic disease of limb bones with calcitonin rather than etidronate, at least for the first course of therapy." We approve of this advice and extend it to all osteolytic cases of Paget's disease, and explain why. In our opinion it was the task of the reviewer to bring these nuances to the reader.

That this restriction applies only to etidronate among the diphosphonates stems from its poor ratio between therapeutic efficacy and local toxicity. Diphosphonates with a better ratio achieve better results. As we recently demonstrated at the Fourth International CEMO symposium, "Diphosphonates and Bone," at Nyon, Switzerland, (3-amino-1-hydroxypropylidene)-1, 1-diphosphonate (APD), administered at a dosage of 600 mg/24 h, seldom induces negative focal radiographic findings. The accompanying table compares several therapeutic regimens, in which positive and negative radiological signs are analysed in accordance with previously indicated criteria.[5] In this study 18 patients have been followed, and data on 17 have been analysed and one was not, owing to a spontaneous fracture of a pagetic tibia after 45 days of treatment. Whether this non-traumatic fracture was related to therapy is unknown. The complete transverse fracture healed in a plaster cast despite continuation of APD therapy. Only those seven patients who had completed six months of the therapeutic trial are included in the table. The constructive index (ratio of positive to negative signs per course of therapy) is infinite for calcitonin since no negative signs were observed, largely positive for APD, almost neutral for combined therapy (calcitonin and etidronate,) and far beneath one for etidronate alone. Analysis of all cases, including that of the non-fractured pagetic tibia of the patient who fractured his other affected tibia, would give the following results for APD: 48 positive signs, 4 negative signs, 6·0 positive signs per course of therapy, 0·5 negative signs per course of therapy, and a constructive index of 12. This is still acceptable, provided that APD has no unwanted extraskeletal side effects.

Positive and negative radiological changes appearing in the pagetic bones as a result of different therapeutic regimens

Treatment	In all cases		Per course of therapy		Constructive index
	Positive signs	Negative signs	Positive signs	Negative signs	
Calcitonin	92	0	6·1	0	
Calcitonin and etidronate	13	14	2·2	2·3	0·96
Etidronate	8	29	0·9	3·2	0·28
APD*	42	2	6·0	0·3	20

*APD = (3-amino-1-hydroxypropylidene)-1,1-diphosphonate.

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[1] Finerman GAM, Gonick HC, Smith RK, Mayfield JM. *Clin Orthop* 1976;**120**:115-24.
[2] Kantrowitz FG, Byrne MH, Schiller AL, Krane SM. *Arthr Rheum* 1975;**18**:407.
[3] Canfield R, Rosner W, Skinner J, *et al. J Clin Endocr* 1977;**44**:96-106.
[4] Nagant de Deuxchaisnes C, Rombouts-Lindemans C, Huaux JP, *et al. Acta Rheumatologica* 1980;**4**:425-57.
[5] Nagant de Deuxchaisnes C, Rombouts-Lindemans C, Huaux JP, Devogelaer JP, Malghem J, Maldague B. In: MacIntyre I, Szelke M, eds. *Molecular endocrinology*. Amsterdam: Elsevier/North-Holland Biomedical Press, 1979:405-33.
[6] Russell RGC, Douglas DL, Duckworth T, *et al.* In: Caniggia A, ed. *Edidronate*. Pisa: Istituto Gentili, 1980:97-120.

Charitable organisations in medical research

SIR,—Mr A Mackie's recent letter (12 December, p 1612) should not be allowed to stand without comment. It must be stated clearly that neither the Association of Medical Research Charities exhibition nor my recent leading article (21 November, p 1348) "shouted" any collective message as Mr Mackie claims. Both reported the ways in which research monies are spent by the charities—and it should be remembered that the manner in which these funds are allocated is largely determined by the public. Mr Mackie clearly disagrees with the way the public exercises its choice and that is his privilege. He has many opportunities to express alternative views—and he might be better engaged developing rational arguments in support of these than in making sententious statements on the researchers' "moral and material duty."

The largest part of Mr Mackie's letter stripped of its intemperate language makes two points. The first is that health education and preventive medicine require additional resources. I agree—and so do many of the charities, which allocated one and a quarter million pounds to health education last year. Further resources should not, however, be provided by reallocating funds dedicated to medical research for the following reasons: (1) Know-