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Parathyroid hormone

SIR, We were astonished that Dunham *et al.*¹ seemed to be ignorant of the work that our group has carried out over the past 10 years concerning the levels of parathyroid hormone (PTH) in haemochromatosis and idiopathic articular chondrocalcinosis.

As early as 1972 we studied the calcium and phosphorus balance in 44 patients with idiopathic haemochromatosis. We discovered an isolated increase in urinary phosphate clearance in nearly 30% of the patients studied. We proposed that idiopathic haemochromatosis may be accompanied by normocalcaemic hyperparathyroidism.² This hypothesis was confirmed in 1974 by radioimmunoassay of the carboxyl fragment of PTH. In 7 out of 27 patients with haemochromatosis PTH levels were elevated.³ In 1975, using the same radioimmunoassay, we compared PTH levels in 22 patients with haemochromatosis to 20 controls. Eleven of the patients with idiopathic haemochromatosis had PTH levels that were greater than the highest level found in the control group ($p < 0.01$, W test).⁴ In 1979 we presented 38 observations on patients with idiopathic haemochromatosis and were able to show that a relationship existed between elevated PTH levels and the onset of clinical signs of arthropathy in younger patients (approximately 40 years old). In contrast PTH levels were significantly less increased ($p < 0.001$, W test) in patients who were a decade older (about 50 years old) and who had roentgenographic evidence of articular chondrocalcinosis (Table 1).⁵

In 1981 we measured PTH levels in 69 patients with idiopathic articular chondrocalcinosis, who were classified

according to whether the diagnosis was considered possible, probable, or certain. They were compared with 57 controls. This radioimmunoassay recognised a sequence between residues 34-84 of the C-terminal fragment. Normocalcaemic hyperparathormonaemia was found in 15 out of 29 patients with 'possible chondrocalcinosis' (average age 39 ± 11 years), in 12 out of 16 patients with 'probable chondrocalcinosis' (average age 55 ± 11 years), and in 7 out of 24 patients with 'certain chondrocalcinosis' (average age 66 ± 11 years).⁶

We have established that in a large number of cases idiopathic haemochromatosis and idiopathic articular chondrocalcinosis share a common metabolic anomaly, normocalcaemic hyperparathormonaemia. These elevated PTH levels may play a key role in the development of osteoarticular changes in these diseases even if increased serum PTH is observed only during a given period, usually early in the evolution. We regret that Dunham *et al.* did not consider it necessary to refer to this body of work. None the less we are pleased that their results confirm both our findings and the hypotheses that we have proposed.

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SIR, The essence of the work published by Pawlotsky and colleagues is that 'normocalcaemic hyperparathormonaemia' occurs commonly in 'idiopathic haemochromatosis and idiopathic articular chondrocalcinosis'. The whole point of our paper was the importance of measuring the biologically active hormone, since, as emphasised by McCarty *et al.*¹ there is considerable doubt as to what even the best radioimmunoassays of parathyroid hormone (PTH) are actually measuring. This

Table 1 Observations on 38 patients with haemochromatosis

Disorders	None	Clinical	X-ray
Group	(1)	(2)	(3)
Number	11	6	21
Age (years)	42 ± 6	40 ± 5	53 ± 9
PTH (ng/ml)	0.82 ± 0.57	1.93 ± 0.59	0.76 ± 0.55

arises particularly from the fact² that the circulating level of PTH, which should be defined as the biologically active hormone and not by an immunological response to unidentified antigenic fragments of PTH or to other molecules which may be unrelated to PTH, cannot be above about 20 pg/ml. Yet even the best generally current radioimmunoassay of PTH cannot measure less than about 150 pg/ml, so that normal levels of 70–450 pg/ml (based on the 1–34 PTH and therefore equivalent to about 140–900 pg/ml of the intact hormone) in an assay based on the biologically active N-terminal region of the molecule,³ are not instructive of the true circulating levels of this hormone. Thus while we were aware of many radioimmunoassays of PTH in these diseases, and of the unwarranted conclusions derived from such studies, we were unwilling to quote more than a few selected examples. We certainly did not wish to give offence by discussing work, such as that by Pawlotsky and colleagues, in which an antibody directed to the C-terminus was used (which detects biologically inactive fragments which have an inordinately long half-time in the circulation⁴) and in which normal circulating levels are recorded in nanograms per millilitre, namely about 500 times more 'PTH' than can actually be circulating. It is on this basis that we made the statement, to which Pawlotsky and colleagues take exception, that our study 'has shown a wide disparity between the circulating levels of biologically active parathyroid hormone and the levels of immuno-reactive hormone previously reported by others'. We consider a 500-fold difference to represent 'a wide disparity'.

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Targeting steroid therapy in rheumatoid arthritis

SIR, As reported previously,¹ we have incorporated dexamethasone palmitate into a lipid microsphere (liposteroid). Like a liposome, the lipid microsphere is easily taken up by phagocytes. Therefore liposteroid accumulates in inflamed tissues and has a much stronger anti-inflammatory activity than free dexamethasone in rats.¹

In order to discover whether or not liposteroid could be used clinically as 'targeting' therapy we carried out a double-blind cross-over test with liposteroid in rheumatoid arthritis. Thirty-six patients with classical or definite rheumatoid arthritis defined by ARA criteria (9 male and 27 female, average age 50.5 years) entered the study. Four types of 1 ml ampoules were prepared: A=liposteroid containing 2.5 mg dexamethasone, B=liposteroid placebo, C=dexamethasone disodium phosphate (Merck) containing 3.3 mg dexamethasone, and D=saline. The patients were treated randomly with 1 ml intravenous injections of either A or B and intramuscular D or C. Two to 3 weeks later they were given B or A and C or D. The effectiveness of steroid was evaluated by the degree and duration of subjective improvement in joint symptoms and morning stiffness and preference of patients for each treatment. In this study the degree of improvement of joint symptoms was arbitrarily recorded as very (++), moderately (+), slightly (±), or not (–) improved, and the preference of patients was also recorded as much better, better, or similar.

The results are shown in Tables 1 and 2. Although the degree of improvement in joint symptoms on 3 days was not so different in the 2 groups, the average duration of effectiveness in joint symptoms and morning stiffness was longer in patients on liposteroid than in those on free dexamethasone. As to the preference of patients for each group, liposteroid was significantly more preferable than free dexamethasone. As shown in Table 2, liposteroid was given first in 17 and free dexamethasone was injected first in 19. However, no difference in superiority of liposteroid was observed between the 2 tests. No particular side effects were observed during the test. In conclusion, liposteroid is

Table 1 Effectiveness of one-shot injection of liposteroid (2.5 mg dexamethasone in lipid microsphere) and 3.3 mg free dexamethasone in 36 patients with rheumatoid arthritis

Symptoms		Liposteroid	Free dexamethasone
Improvement of joint symptoms 3 days after the injection	++	9	6
	+	17	16
	±	5	5
	=	5	9
Duration of effectiveness in joint symptoms (mean±SE)*		9.1±1.1 day	5.7±0.8 day
Duration of effectiveness in morning stiffness (mean±SE)		2.9±0.8 day	1.6±0.5 day

*p<0.05 (t-test).