SHORT REPORTS

Simultaneous measurement of a deficit in total body calcium and phosphorus in diagnosis of hyperparathyroidism

Bone disease is a well-established complication of primary hyperparathyroidism but may not be detected early by conventional clinical and radiological procedures because of their limited sensitivity.¹ Nevertheless, sequential changes in body calcium estimated by activation analysis *in vivo* and expressed in relative terms have been reported after parathyroidectomy.^{2,3} Using an analogous procedure, we have measured the total body content of calcium, phosphorus, sodium, chlorine, potassium, and nitrogen simultaneously in absolute terms (mmol or g).⁴ We report a patient in whom an appreciable depletion of calcium and phosphorus was not detected radiologically, and hyperparathyroidism was later confirmed by removal of a parathyroid adenoma.

Case report

A 62-year-old woman presented with septicaemia and acute renal failure secondary to a right ureteric calculus. Investigations after recovery showed persistently raised serum calcium and alkaline phosphatase concentrations, a renal tubular phosphate leak, and a raised serum parathyroid hormone concentration of 750 ng/l (normal range 0-550 ng/l). Biochemical findings are summarised in the table. Skeletal survey showed no diagnostic abnormalities, nor did initial iliac crest trephine biopsy.

The patient was examined by activation analysis (table).⁴ Her height and weight were used to derive "normal" values based on our findings in patients with unrelated diseases. The measured values of total body sodium, chlorine, potassium, and nitrogen were similar to the expected normal values, but those for calcium and phosphorus were about 68% of the expected ones, outside the normal range. These findings suggested a genuine depletion of bone mineral, despite the lack of radiological evidence. Nevertheless, a review of the histological features of the iliac crest trephine biopsy specimen was not incompatible with a diagnosis of primary hyperparathyroidism. The case was then reviewed in detail and at exploratory operation a mixed chief and oxyphil cell parathyroid adenoma was removed.

Biochemical findings in a patient with unsuspected bone disease and hyperparathyroidism

Biochemical findings						
Ca (mmol/l)	P (mmol/l)	Albumin (g/l)	Alkaline phosphatase (IU/l)	Phosphate clearance (ml/min)		
3.00	1.10	44	324	15.8		
Total body findings						
	Ca (g)	P (g)	Na (g)	Cl (g)	N (g)	K (g)
Measured	546	317	55	61	1234	75
Expected "normal"	805	460	56	56	1290	78

Conversion: SI to traditional units—Ca: 1 mmol/l $\approx$ 4 mg/100 ml. P: 1 mmol/l $\approx$ 3.1 mg/100 ml.

Comment

Hosking *et al*² described two patients in whom sequential measurements made before parathyroidectomy showed a progressive decrease in body calcium of about 13% and 30% of the initial value. They were unable to measure body calcium in absolute terms and could not therefore define the initial bone state of their patients. Cohn *et al*³ measured body calcium and phosphorus in grams but, normalising the values to height, found no evidence of deficiency in four patients with hyperparathyroidism. Nevertheless, our analysis of their results for body calcium, normalised either to body potassium or to body nitrogen, is consistent with a bone mineral deficiency.

In our case it was clearly an advantage to express the total body content of the measured elements in absolute terms. Using activation analysis we detected a deficit in bone mineral not found by conventional radiology, thus providing strong evidence of hyperpara-

thyroidism. We shall measure total body calcium and phosphorus again to determine whether the bone mineral is being restored. The incidence of osteitis fibrosa cystica generalisata in primary hyperparathyroidism has been quoted as between 10% and 25% and recently as even less.⁵ The true incidence of osteitis fibrosa may be higher when more sensitive and quantitative techniques such as activation analysis are used.

Requests for reprints should be sent to Dr Keith Boddy.

¹ Rasmussen, H, *American Journal of Medicine*, 1961, **30**, 112.

² Hosking, D J, *et al*, *Clinical Science*, 1972, **43**, 627.

³ Cohn, S H, *et al*, *Journal of Laboratory and Clinical Medicine*, 1972, **79**, 978.

⁴ Boddy, K, *et al*, *Clinical Science and Molecular Medicine*, 1978, **54**, 187.

⁵ Harrison, O O, *Principles of Internal Medicine*, 8th edn, p 2016. New York, McGraw-Hill, 1977.

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Soft tissue sarcomas and intramuscular injections: an epidemiological survey

Intramuscular iron preparations, such as iron-dextran, and aluminium compounds, such as those used in desensitising injections, have induced sarcomas in animal studies.^{1,2} The relevance of these studies to the aetiology of soft tissue sarcomas in man is uncertain. Descriptions of sarcomas developing in sites where iron had been injected from several months to 13 years earlier³ suggest there may be a causal relationship between intramuscular injections and sarcoma formation in some patients, while in a recent study of eight patients with soft tissue sarcomas neither clinical nor histological evidence for such a relationship could be found.⁴ Furthermore, no increase was found in the incidence of sarcomas in the arm since the introduction in Connecticut, USA, of alum-adsorbed allergenic extracts.⁵ On the other hand, epidemiological studies of this sort are few.

In a retrospective survey of patients in the Trent region who presented in the years 1974 and 1975 with soft tissue sarcomas we have determined the frequency with which tumours appear in sites where injections are normally given. We have examined all available clinical records of those patients in whom tumours developed in these sites for evidence of past parenteral treatment which would lend support to such a causal relationship.

Methods and results

The Trent Regional Cancer Registry provided the names and hospital numbers of patients with soft tissue sarcomas presenting in 1974 and 1975. Those with tumours of the trunk were not studied further. More detailed information about the patients with limb tumours, including their age and sex and the precise site and diagnosis of their tumour, was obtained from hospital case notes. Family practitioner records for those patients whose tumours had arisen in sites where injections might have been given were examined for details of past injection treatments. Full confidentiality was maintained throughout.

The results are shown in the table. We traced the hospital records of 46 of the 49 patients with leg tumours. There were 28 women and 18 men with a mean age of 48.2 (range 4-86). Three patients were under 10 years old and 17 patients had tumours either at the level of the knee or below. One patient had von Recklinghausen's disease, which is known to predispose towards sarcoma formation, and she had developed a neurosarcoma. Twelve patients (seven women) had tumours in sites where injections might have been given (that is, the buttock and upper anterior, posterior, and lateral aspects of the thigh), representing 26% of all evaluable patients with leg tumours. Only two tumours, 4% of those in the leg, arose in the buttock. We examined the family practitioners' records of all these patients and found no history of allergy or iron deficiency or of previous treatments by injections of any sort.

We traced the hospital records of 19 of the 23 patients with arm tumours. There were 11 women and eight men with a mean age of 49.8 (range 17-82). Five patients had tumours in sites where injections might have been given (that is, the deltoid region and anterior and posterior aspects of the upper arm), representing 26.3% of all evaluable patients with arm tumours. We examined the family practitioners' records of all these patients and again found no history of allergy or iron deficiency, or of previous treatments by injections of any sort.

Soft tissue sarcomas, Trent Region 1974-5

	Leg	Arm
Total number	49	23
Hospital case records examined	46	19
Likely injection sites	12	5
Unlikely injection sites	34	14

Comment

This study does not support the suggestion of a causal relationship between sarcoma formation and intramuscular injections. Conclusions drawn from such a study may be criticised since case records may be incomplete. Nevertheless, we found evidence neither of injection treatments being used nor of conditions for which they might have been used. Thus no patients had long-standing anaemia for which iron injections might be given or had chronic asthma for which courses of desensitising injections might have been given. If iron injections had been given, but not recorded, and had a tendency to induce sarcomas, then one would have expected the proportion of tumours arising in likely injection sites to be greater in the leg than in the arm, for this treatment is generally (if not always) given into the buttock—but this was not the case.

To obtain more precise information would be difficult. If patients with sarcomas were to be questioned themselves then this would have to be done soon after diagnosis. Patients are often unknown to cancer registries before they die, and it would be time consuming for an individual to collect sufficient patients, for the disease is rare. An alternative would be to follow up patients known to have had injection treatments. In 1974 there were respectively 95 900 and 45 000 intramuscular iron injections and desensitising injection courses given in the country. Reducing these figures for the population of the Trent Region (4.5 million at that time) would suggest that 8000 people were receiving courses of intramuscular iron preparations and 4000 people desensitising injections a year. The risk of cancer is likely to be very small and the latent interval long, so that again this would pose considerable organisational problems. Our investigations and others suggest that such studies are likely to be unprofitable.

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² Macfarlane, J O, Federal Drug Administration Bureau of Biologics, *Report*, 75, 2. Springfield, Virginia, US Department of Commerce, 1974.

³ Greenberg, G, *British Medical Journal*, 1976, **1**, 1508.

⁴ Weinreb, K, Salm, R, and Greenberg, G, *British Medical Journal*, 1978, **1**, 683.

⁵ Jekel, J F, Freeman, D H, and Meigs, J W, *Annals of Allergy*, 1978, **40**, 28.

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PUVA-induced suppression of contact sensitivity to mustine hydrochloride in mycosis fungoides

The major complication of topical treatment with mustine hydrochloride (nitrogen mustard) is contact dermatitis. Patients developing such contact sensitivity often experience more benefit from the drug, leading to long-lasting remissions, but the occurrence of contact dermatitis often precludes further use of mustine. When this occurs an alternative treatment is psoralen (8-methoxy-psoralen) plus long-wave ultraviolet light (PUVA).

We have observed that contact sensitivity to mustine has diminished after PUVA in five cases of mycosis fungoides.

Case reports

Five patients with mycosis fungoides, aged between 55 and 71, were treated with daily topical whole body application of mustine, 10 or 20 mg in 50 ml water. Their disease had lasted from four to 30 years and the individual stage one to two years. In two patients the disease was at the plaque stage and in three at the tumour stage. After two to three weeks' treatment all patients developed severe dermatitis, which prevented further application of mustine. In case 1 the dermatitis could initially be controlled with topical hyposensitisation with mustine,¹ but when the intervals between the applications were prolonged the mycosis fungoides relapsed and intensified mustine treatment then provoked sudden severe contact urticaria accompanied by bronchial asthma. In three patients PUVA treatment was started within one month after stopping mustine, while in two there was an interval of three and four years. After eight to 16 months' PUVA treatment open patch tests with mustine showed that the sensitivity had now disappeared (table). In case 2 the nitrogen mustard could be started again without any contact reaction.

Results of patch testing in five patients with mycosis fungoides who were sensitised to nitrogen mustard and treated with PUVA

Case No:	1	2	3	4	5
PUVA					
Total dose (J/cm ²)	104	335	384	97	48
Threshold concentration of mustine (mg/l water)					
Before PUVA	0.15	0.15	0.7	5.0	5.0
After PUVA	30	100	100	30	30

Patch tests with nitrogen mustard—Serial dilutions of mustine in water were applied, uncovered, to the upper back and the tests read after 20 minutes, eight, 24, and 48 hours. The threshold concentration of erythematous reaction is given in the table. All patients were extremely sensitive to mustine, resulting in delayed type test reactions to weak concentrations. After PUVA treatment, however, the patients did not react to even the strongest concentration of mustine. In case 1 the patch test before PUVA resulted in an immediate type reaction to the weakest concentration of mustine used. After treatment with PUVA retesting showed a delayed type reaction to the highest concentration of nitrogen mustard.

Patch tests with DNCB—In cases 4 and 5 sensitisation was induced by dinitrochlorobenzene (DNCB), 0.5 mg, resulting in a threshold concentration of 0.05 mg DNCB/ml acetone at challenge. After PUVA the threshold concentration was unchanged.

Comment

Contact sensitisation to mustine is beneficial in clearing cutaneous mycosis fungoides, but patients often find the complications intolerable and so the treatment has to be withdrawn. This contact dermatitis is commonly considered to be of the delayed type,² even if contact urticaria has been described.³

In cases of sensitisation to mustine PUVA is an alternative.⁴ Our finding that contact dermatitis to mustine can disappear during treatment with PUVA is new. The possibility of spontaneous diminution in the contact reaction has to be considered. Nevertheless, unchanged reactivity to mustine three to four years after the initial sensitisation has been observed in another four cases (unpublished observations). A practical implication of the suppression phenomenon is that patients sensitised to mustine after PUVA can resume topical application of the drug.

We have no explanation of this phenomenon. Frosch and Kligman⁵ saw inflammatory reactions to dimethylsulphoxide reduced after treatment with PUVA, indicating an effect on non-allergic inflammatory mechanisms. The fact that the DNCB reaction was unaltered