were therefore disappointed that no mention was made of the use of mithramycin in the management of hypercalcaemia in these patients, as the following case illustrates.

A 53-year-old woman was admitted to hospital with a nine-month history of bone pain. Bence Jones myeloma was diagnosed on the basis of a marrow aspirate, "K" type light chains in the serum, and "K" type Bence Jones proteinuria. On admission she was dehydrated, with nausea and vomiting. Serum calcium was 3·8 mmol/l (15·2 mg/100 ml), serum phosphate 1·4 mmol/l (4·5 mg/100 ml), and blood urea 15·4 mmol/l (93 mg/100 ml). A skeletal survey showed widespread lytic bone deposits. The hypercalcaemia was treated initially with intravenous saline infusions of 3 l/day with potassium chloride supplements, restriction of dietary calcium, and hydrocortisone infusions of 100 mg six-hourly (later substituted with prednisolone 45 mg/daily once vomiting had stopped). Treatment for myeloma was started with cyclophosphamide 50 mg/daily. None of this therapy made any significant impression on the hypercalcaemia (fig. 1). The patient was therefore given a single intravenous injection of mithramycin 1 mg. This was well tolerated without side effects. The serum calcium fell rapidly within 24 hours to 2·9 mmol/l (11·8 mg/100 ml) around which it remained for five days before rising again (fig. 1).

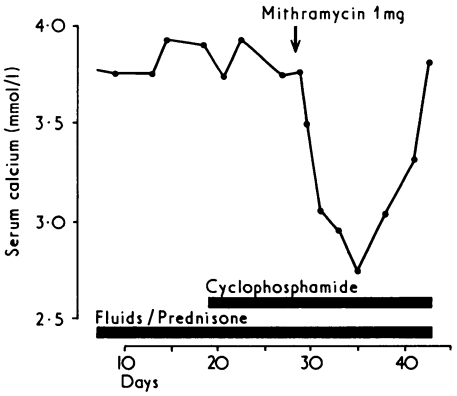

FIG. 1.—Response of hypercalcaemia to therapy in a 53-year-old woman with myeloma.
Conversion: SI to Trdaitional Units—Serum calcium 1 mmol/l ≃ 4 mg/100 ml.

We have also used mithramycin successfully in the treatment of hypercalcaemia associated with breast carcinoma and lymphoma. Like others,[2 3] we have found the response in all instances to be rapid, effective, and maintained for four days or longer after a single intravenous injection of 20 μg/kg (1-1·5 mg total dose) (fig. 2). In our experience it is unnecessary to repeat the therapy for at least four days, and at this dosage (about one-fifth to one-tenth of the recognized antitumour dose) significant marrow depression and a dose-related haemorrhagic syndrome[4] do not occur. Mithramycin probably corrects hypercalcaemia by inhibiting excessive bone resorption and is therefore unlikely to cause metastatic calcification.[5]

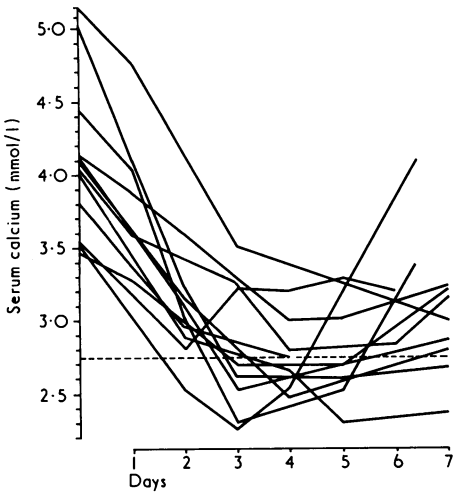

FIG. 2.—Effect of single intravenous injection of mithramycin 20 μg/kg in 12 episodes of hypercalcaemia associated with malignancy.

We therefore think that the rapid, effective, and prolonged action of mithramycin on serum calcium with absence of side effects in correct dosage makes it the treatment of choice in hypercalcaemia associated with myeloma and other malignant conditions in which dietary restriction, fluids, and prednisone alone prove ineffective.—We are, etc.,

I. E. SMITH
T. J. POWLES

Royal Marsden Hospital and Institute of Cancer Research,
Sutton, Surrey

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Management of Lithium Treatment

SIR,—We are surprised at the nature and content of Dr. J. L. Crammer's letter (16 November, p. 408). The original subject of our discussion was the practical management of lithium treatment; it seems irrelevant to widen the controversy by including a separate issue—namely, the extent of lithium excretion following discontinuation of the drug. Since the subject has been raised, it is necessary for us to reply.

Dr. Crammer saw fit to refer to his failure to confirm previous findings from this unit[1] that some patients, previously treated with lithium, excrete small amounts of the cation in the urine at intermittent intervals after the drug has been discontinued. We agree that metabolic balance work over long intervals is difficult to control, especially in psychiatric patients, and that continuity of trained and experienced nursing staff in adequate numbers is essential as Dr. Crammer rightly insists. However, we are satisfied that the results obtained were not due to artefacts for the following reasons. (1) Lithium appeared in the blood plasma as well as in the urine during some of these episodes, thus excluding contamination of urine by patients or staff of the kind to which Dr. Crammer refers. (2) The possibility of unauthorized ingestion of lithium salts by the patients was meticulously investigated after the initial findings and careful precautions were taken to exclude this possibility. Nevertheless, a number of further cases of intermittent lithium excretion occurred even under these very rigorous conditions. (3) The total amount of lithium excreted in each discrete episode, though significant, was not compatible with the ingestion of a single dose of aqueous lithium citrate (8 mmol (mEq)) which was the form in which the lithium was being administered in our balance studies; nor was it compatible with the amount of lithium in the smallest tablet commercially available.

We believe that the results are genuine and probably occur as a result of bone resorption, since it has been shown that lithium accumulates in bone[2] and that one fraction is tenaciously retained within the bone after discontinuation of treatment.[3]

Dr. Crammer also questions our findings that some subjects taking slow-release lithium carbonate tablets have larger amounts of lithium in their stools than we previously reported when aqueous lithium salts were administered.[1] The results of our investigation in 20 subjects (patients and normal volunteers) reported in preliminary form[4] will be published with full details of the kind desired by Dr. Crammer. This study involved the oral ingestion of a single 1-g dose of various commercial lithium carbonate tablets by subjects who had either never received lithium previously or had not done so for at least one month. The plasma and urinary excretion patterns of lithium were determined for the following 24 hours and faeces collected for periods of 1-8 days. The percentage of the lithium dose recovered in the faeces varied from 5 to 33% for Phasal, 1 to 6% for Priadel, and 5 to 7% for Camcolit. The subjects with high values of faecal lithium excretion on Phasal showed low plasma and urinary lithium concentrations, indicating incomplete lithium absorption.

Dr. Crammer and his colleagues (14 September, p. 650) have clearly shown that delaying stomach emptying time affects the absorption of lithium and we accept that gastrointestinal function influences the plasma lithium level. Our point is that the two "sustained-release" preparations used in Britain (Priadel and Phasal) do not work as they imply (p. 652) by preventing absorption in the acid conditions of the stomach and allowing release in the more alkaline conditions of the small intestine. Priadel and Phasal both consist of lithium carbonate embedded in an inert matrix and their "sustained-release" properties are based on the slow dispersion of the matrix, largely *irrespective* of the pH of the surrounding solution. This statement is based on the manufacturers' information about their tablets, not on our in vitro work, which we agree may not necessarily correspond with the situation in the body. We hope this has clarified the issues.—We are, etc.,

R. P. HULLIN
S. P. TYRER

Metabolic Research Unit,
High Royds Hospital,
Ilkley, Yorks

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Clonazepam in the Treatment of Drug-induced Dyskinesia

SIR,—In a report on a clomipramine infusion unit[1] I described the use of diazepam as a method of controlling the dyskinesia produced in patients given the infusion in doses of 150-200 mg. The diazepam was effective but had very definite drawbacks, as frequently the oral dose had to be raised to 10 mg three times a day so that they became drowsy and dulled.

Recently clonazepam has been introduced for the treatment of epilepsy[2 3] and reports in