treated in this way. Surface abscesses were also drained when aspiration failed to clear them.

We would like to emphasize these points so as to spare any disappointment to our colleagues in the tropics when they are faced, as they will be, with such situations.—We are, etc.,

St. Ola,
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ARY BLESOVSKY

¹ Konstam, P. G., and Blesovsky, A., *British Journal of Surgery*, 1962, 50, 26.

SIR,—Your leading article on this subject (4 December, p. 613) was no doubt justified by the recent reports you quoted. There was, however, one outstanding flaw in your review which was to my mind almost criminally negligent. You did not draw attention to the fact that it was in the cases treated in an ambulant manner that paraplegia developed during treatment. I feel that you should draw attention to this and that any one treating tuberculosis of the spine in the ambulant manner for the first time should confine his experiment to patients with the disease located below the termination of the dura and particularly not in the dangerous vertebrae, dorsal 4-8.—I am, etc.,

RANDLE LUNT

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** Mr. Lunt has done well to draw attention to spinal cord involvement in tuberculosis of the spine. Because of limitation of space the leading article to which he refers dealt almost solely with healing of the vertebral disease. However, Mr. Lunt, as a consultant in orthopaedic tuberculosis, will certainly have studied the four reports referred to, even though he has drawn conclusions diametrically opposed to the evidence that they showed.

Of 268 followed-up patients treated as ambulant outpatients, three who had been free from central nervous signs on admission to the trials developed paraparesis. None became unable to walk. Two recovered completely on ambulant chemotherapy alone and the third after an operation which hindsight suggests might have been unnecessary. Mr. Lunt will recollect that the leading article did not advise ambulant chemotherapy as the sole method of treatment in circumstances in which radical surgery is safe. When he has demonstrated, not merely implied or asserted, that any other method of treatment produces a lower incidence of paraplegia his charge of "almost criminal" negligence in recommending ambulant treatment in places where surgical facilities are scarce will call for an answer. On the evidence of the Medical Research Council's reports it does not do so at present.—Ed., *B.M.J.*

Cyclophosphamide in Treatment of Nephrotic Syndrome

SIR,—We would like to comment on the excellent article by Professor J. S. Cameron and others (5 October, p. 7). They reported sustained remission after cyclophosphamide treatment in 20 out of 58 children

with corticosteroid-sensitive but relapsing nephrotic syndrome and "minimal-change" lesions on renal biopsy.

We recently reported¹ the results of short-term cyclophosphamide therapy in 13 adults and four children presenting with the nephrotic syndrome or persistent proteinuria, normal renal excretory function, and either mild but definite glomerular lesions (14 patients) or no glomerular abnormalities on light microscopy (3 patients). Sustained remission of proteinuria for 5-22 months (mean 12.7 months) was obtained in 11 of the 17 patients and clinical improvement seen in four other patients. The onset of remission was usually prompt (within three months of starting treatment in nine patients). The response was independent of the duration of disease and histological diagnosis—60-75% of patients with focal proliferative glomerulonephritis, diffuse proliferative glomerulonephritis, and mesangiocapillary glomerulonephritis obtaining complete remission. Two patients conceived normal children after cyclophosphamide treatment. In only one patient, aged 14, was amenorrhoea seen seven months after therapy.

We suggest that cyclophosphamide given for a short period has a definite role in patients with glomerular lesions other than minimal change and that short-term therapy may avoid the reported toxicity to gonadal function.—We are, etc.,

L. S. IBELS
A. A. PALMER
J. F. MAHONY
J. H. STEWART

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Sydney Hospital,
Sydney, Australia

¹ Ibels, L. S., et al., in *Drugs and the Kidney*, ed. K. D. G. Edwards. *Progress in Biochemical Pharmacology*, vol. 9, Basel, Karger, 1974.

Fish Tank Granuloma

SIR,—A woman aged 46 cut her hand cleaning a fish tank. After 12 months a small unhealed lesion remained over the head of the fourth metacarpal. No foreign body was found on exploration. Some weeks later the back of her hand and wrist became swollen. At operation a chronic thickened synovium of the extensor tendon was excised. No bacteriological examination was made, but sections of a substantial portion of the thickened synovial tissue showed a granulomatous reaction with small numbers of giant cells but no caseation or necrosis. No acid-fast bacilli were found. Urine, E.S.R., and chest radiograph were all normal. After the biopsy a comparative skin test was carried out using five units of tuberculin (P.P.D.) and an equivalent dose of *Mycobacterium marinum* antigen. Induration 20 mm in diameter resulted from the latter but less than 6 mm from the P.P.D.

Myco. marinum lives in water and is an opportunist pathogen of aquatic animals, including man in the role of swimmer or keeper of pet fish. Risks from it in the latter hobby have been noted.^{1,2} The organism grows very poorly at 37°C, and presumably for this reason human infections are always cutaneous. They present in two main ways: (1) as indolent localized but sometimes extensive lesions of the skin, first papular and then nodular, which may become verrucous or may develop pustules or liquefying granulomata; (2) a sporotrichoid-like infec-

tion initially seen at the site of an injury but followed by the lymphatic spread of skin lesions, which may be nodules or abscesses and from the hand may reach to the axilla.

The present case is of interest because a rather trivial lesion was activated by surgical exploration and the extension of inflammation resulted in tenosynovitis, a complication which appears not to have been previously recorded and which represents a deeper incursion into the tissues than is usual. Histology of the synovium suggested the possibility of a *Myco. marinum* infection and prompted the skin test, which strongly supported the hypothesis. Unfortunately the connexion of indolent skin lesions with aquaria is still not generally known. An initial bacteriological examination and skin test in this case would have led to effective treatment and saved two operations. Perhaps recognition would be helpful by encouraging the memorable name "fish tank granuloma," which has been suggested for the condition.—We are, etc.,

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J. MARKS

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Cardiff

¹ *British Medical Journal*, 1970, 2, 438.

² Barrow, G. I., and Hewitt, M., *British Medical Journal*, 1971, 2, 505.

Complication of Austin Moore Prosthesis

SIR,—I read with interest the letter of Mr. O. N. Vyas and Mr. A. K. Varshneya (14 December, p. 658), and I am surprised to hear that insertion of the Austin Moore prosthesis is performed in some centres under x-ray control. Surely this is unnecessary as this procedure is virtually performed under direct vision.

This point, therefore, leads to a comment on the purpose of their letter—namely, the insertion of a probe into the femur. If the femoral shaft is carefully reamed out the alignment of the reamer is readily checked and thus will ensure that it passes along the line of the femur. Similarly, the shaft of the femur below the trochanter may be palpated while reaming and when the prosthesis is being inserted. The problem of lateral protrusion of the stem is thus easily avoided. I therefore feel that this additional step seems unnecessary in an operation that has been performed on countless occasions in different parts of the world.—I am, etc.,

M. I. B. BESSER

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London S.E.13

Mithramycin for Hypercalcaemia Associated with Myeloma and other Malignancies

SIR,—In his review of myelomatosis Dr. J. S. Malpas (30 November, p. 520) recommends that neutral phosphate be used to treat associated hypercalcaemia when dietary restriction, fluids, and prednisone prove ineffective. Oral phosphate is, however, impractical if the hypercalcaemic patient is nauseated or vomiting and intravenous phosphate infusion carries the risk of ectopic calcification, which may prove fatal.¹ We

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 Traditional Units—Serum calcium 1 mmol/l $\approx$ 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 μ g/kg (1.15 mg total dose) (fig. 2). In our ex-therapy for at least four days, and at this dosage (about one-fifth to one-tenth of the

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

perience it is unnecessary to repeat the recognized antitumour dose) significant marrow depression and a dose-related haemorrhagic syndrome⁴ do not occur. Mithramycin probably corrects hypercalcaemia by inhibiting excessive bone resorption and is therefore unlikely to cause metastatic calcification.⁵

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.,

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T. J. POWLES

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- 1 Breuer, R. I., and Le Bauer, J., *Journal of Clinical Endocrinology and Metabolism*, 1967, 27, 695.
- 2 Perlia, C. P., et al., *Cancer*, 1970, 25, 389.
- 3 Harrington, G., et al., *New England Journal of Medicine*, 1970, 283, 1172.
- 4 Monto, R. W., et al., *Cancer Research*, 1970, 29, 697.
- 5 Singer, F. R., et al., *New England Journal of Medicine*, 1970, 283, 634.

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 unit¹ 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 bone² 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 form⁴ 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.,

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- 1 Hullin, R. P., et al., *British Journal of Psychiatry*, 1968, 114, 1561.
- 2 Birch, N. J., and Hullin, R. P., *Life Sciences*, p. 2, 1972, 11, 1095.
- 3 Birch, N. J., *Clinical Science and Molecular Medicine*, 1974, 46, 409.
- 4 Birch, N. J., et al., *British Journal of Clinical Pharmacology*, 1974, 1, 339.

Clonazepam in the Treatment of Drug-induced Dyskinesia

SIR,—In a report on a clomipramine infusion unit¹ 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