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I. L. EVANS, M.B., CH.B., M.R.C.P.GLASG., M.R.C.P.ED.,
Late Medical Registrar, Royal Infirmary, Glasgow C.4.

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Mithramycin Treatment of Malignant Hypercalcaemia

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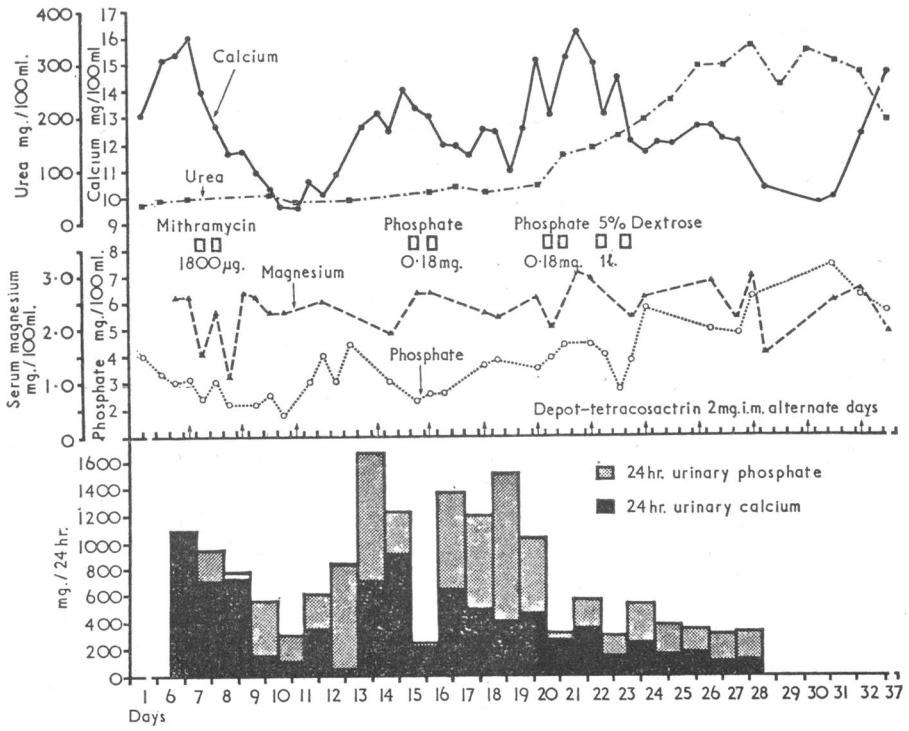
Mithramycin is an antibiotic with anti-tumour activity similar to actinomycin D. Hypocalcaemia has been reported following its use (Brown and Kennedy, 1965), and it has been suggested that it should be given in the emergency treatment of hypercalcaemia, particularly when associated with malignant disease (Parsons *et al.*, 1967 ; Baum, 1967). We report the findings in a patient with malignant hypercalcaemia treated in this way.

CASE REPORT

In 1963 a 47-year-old woman underwent a left radical mastectomy, followed by radiotherapy, for a stage 3 anaplastic carcinoma of the breast. In 1965 secondary deposits in the thoracic and lumbar spine and pelvis were treated with bilateral oophorectomy, local radiotherapy, androgens (fluoxymesterone and nandrolone), and prednisolone for eight months. In January 1967 further irradiation of the pelvis and upper femora was necessary. In May 1967 she was readmitted with severe pain in the lower back and legs, having been confined to bed since January and requiring opiates for control of her pain. On this admission her serum calcium was 7.7 mg./100 ml. and serum phosphorus 3.4 mg./100 ml. She was given blood transfusion and prednisolone, 30 mg. daily. As the pain was not relieved prednisolone was replaced after two weeks by intramuscular long-acting synthetic β^{1-24} corticotrophin (depot-tetracosactrin), 1 mg. on alternate days (Besser *et al.*, 1967). The pain rapidly disappeared and within a month she was mobilized and discharged, able to walk without sticks. In September 1967, after four days of nausea, vomiting, and headache, she was found to have hypercalcaemia and was readmitted.

Investigations on Admission.—Serum calcium 13.1 mg./100 ml. ; phosphorus 4.0 mg./100 ml. ; magnesium 2.6 mg./100 ml. ; alkaline phosphatase 8 K.A. units/l. ; bilirubin 0.8 mg./100 ml. ; aspartate aminotransferase 38 units/l. ; proteins and electrophoretic pattern normal ; urea 36 mg./100 ml. ; potassium 4.6 mEq/l. ; sodium 131 mEq/l. ; chloride 85 mEq/l. ; bicarbonate 35 mEq/l. ; haemoglobin 12.1 g./100 ml. ; white cell count 6,000/cu. mm., differential normal ; urinary calcium excretion 1,180 mg./24 hours ; phosphorus 946 mg./24 hours ; creatinine clearance 42 ml./min. ; urine analysis —trace of protein, no glycosuria, bacteriologically sterile.

The dose of depot-tetracosactrin was increased to 2 mg. on alternate days, but nevertheless the serum calcium rose to 16.0 mg./100 ml. Therefore mithramycin was administered. Two doses were given on consecutive days: 25 μg./kg. (1.8 mg.) was infused intravenously over eight hours in 1 litre of 5% dextrose on each day. There was a rapid fall in serum calcium and magnesium and in urinary calcium and phosphate excretion (see Chart), and a smaller fall



Changes in serum calcium, magnesium, phosphate, and urea and in urinary calcium and phosphate excretion in a patient treated with intravenous mithramycin, phosphate, and 5% dextrose.

in serum phosphorus and potassium. However, the serum calcium began to rise again after 48 hours. Since it had been noted that the mithramycin contained a small quantity of phosphate as a buffer (as the disodium hydrogen salt), it was decided to give the same quantity of phosphate without the mithramycin. In fact 0.18 mg. of sodium dihydrogen phosphate was infused in 1 litre of 5% dextrose over eight hours on two consecutive days, and this was repeated five days later. Each time there was a significant fall in both the serum calcium and magnesium, though this was less than that seen after mithramycin. Urinary calcium and phosphorus excretion was also reduced. One litre of 5% dextrose was later given alone on two occasions, but by this time any change in serum calcium was masked by the effects of a progressive rise in serum urea. The uraemia was treated with protein withdrawal and intravenous glucose. Despite maintaining a urinary volume of 1.5–2 l./day the patient deteriorated and died five weeks after admission.

Throughout the above regimen the depot-tetracosactrin was continued and the hypokalaemia was treated with potassium supplements (52–78 mEq/day). Plasma cortisol concentrations (Mattingly, 1962) were followed between days 4 and 9, during which time the patients received two doses of 2 mg. of depot-tetracosactrin. While the plasma cortisol level varied from 14 to 70 μg./100 ml., this was in no way correlated with any change in serum calcium. At no time was there any evidence of mithramycin-induced marrow depression.

Necropsy.—Disseminated carcinomatosis, nephrocalcinosis, and acute renal tubular necrosis with metastatic calcification of the alveolar walls and pulmonary arteries were seen. There was no evidence of parathyroid hyperplasia.

Discussion

The rapid fall in serum calcium after mithramycin is in agreement with the findings of Parsons *et al.* (1967) in normocalcaemic and mildly hypercalcaemic patients with malignant disease. Since this fall coincided with a marked diminution in urinary calcium and phosphorus excretion, it seems probable that the fall in circulating calcium was due, at least in part, to sequestration in the soft tissues or bone. However, since no faecal calcium measurements were made, a change in excretion by this route cannot be ruled out. The changes noted are, however, identical with those seen after administration of phosphate alone (Hebert *et al.*, 1966), after which faecal calcium is reduced.

Administration of the small amount of phosphate in 5% dextrose was followed by a fall in serum calcium of approximately 40% of that produced by mithramycin plus phosphate buffer. Since it was difficult to account for this change on physicochemical principles, the effect of 5% dextrose alone was investigated. However, in view of the progressive uraemia it is not possible to interpret the results.

It has been suggested that with mithramycin there are no risks of ectopic calcification or renal damage (Baum, 1967), though Brown and Kennedy (1965) did note the development of proteinuria and a rise in the blood urea in occasional normocalcaemic patients. In our patient the creatinine clearance of 42 ml./min. on admission suggested the presence of some pre-existing renal damage. However, the rapid rise in blood urea indicated that the nephrocalcinosis and pulmonary calcification might have been the result of treatment with the mithramycin itself, or the contained phosphate, rather than the hypercalcaemia.

Parsons *et al.* (1967) gave a continuous infusion of 25 μg. of mithramycin per kg. daily for eight days. In three out of their 16 patients administration had to be stopped prematurely owing to severe vomiting. Our patient received treatment with this drug on only two days and her nausea and vomiting stopped at the end of the first eight-hour infusion, by which time the serum calcium had fallen from 16.0 to 13.9 mg./100 ml.

While mithramycin is highly effective in reducing the serum calcium in malignant hypercalcaemia, as with phosphate treatment (Breuer and LeBauer, 1967), there appears to be a danger of associated nephrocalcinosis and renal failure.

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C. R. W. Edwards, M.B, B.CHIR.,
G. M. Besser, M.D., B.SC., M.R.C.P.,
Medical Professorial Unit, St. Bartholomew's Hospital, London E.C.1.

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