phosphorylase b, except at a tenth of the normal rate. Activation of phosphorylase b, however, was restored to normal by addition of mouse muscle homogenates containing protein kinase but deficient in phosphorylase kinase. This therefore suggests a reduction in protein kinase activity in this patient's muscles. Similarly in the mother in the present study the defect involved in triglyceride breakdown in adipose tissue may possibly be located at the protein kinase involved in the activation of triglyceride lipase. This defect may be on a familial basis since her obese daughter with a hyperlipaemia also showed a reduction in glycerol release from her adipose tissue on stimulation with isoprenaline, despite normal rises in tissue levels of cyclic-AMP. Further work is being conducted to clarify the exact nature of the defects in mobilization of triglycerides from adipose tissue in these two patients. It should be finally emphasized that this defect is likely to be of rare occurrence and is therefore likely not to be an aetiological factor in most overweight patients.

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MEDICAL MEMORANDA

Stilboestrol Diphosphate in Hypercalcaemia due to Parathyroid Carcinoma

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Parathyroid carcinoma is a rare cause of primary hyperparathyroidism. Complete surgical excision of the tumour is often difficult and local recurrence is common; metastases may occur many years later. These tumours are usually resistant to radiotherapy. Medical management of the hypercalcaemia is also difficult and the patient usually dies of hypercalcaemic crisis or of renal failure.

In the case described here severe hypercalcaemia was not controlled by phosphate, synthetic human calcitonin, mithramycin, glucagon, or multiple cytotoxic therapy but responded to stilboestrol diphosphate.

Case Report

A man aged 53 presented in 1968 with pathological fractures and widespread bone pain. His serum calcium was 8·5 mEq/l. and alkaline phosphatase 60 K.A. units. Radiographs showed osteitis fibrosa cystica. In December 1968 a parathyroid tumour, which was adherent to the oesophagus, was removed. It weighed 5 g and its histology was that of a parathyroid carcinoma invading surrounding tissue. The patient's serum calcium reverted to normal and he remained in good health until early in 1971, when bone pains recurred associated with thirst, polyuria, and nausea.

He was referred to us in October 1971, when he looked ill, complained of generalized bone pains, and had bone tenderness. Investigations were: serum calcium 8·5 mEq/l., inorganic phosphate 1·8 mEq/l., alkaline phosphatase 85 K.A. units mainly of bony type (normal < 13), total acid phosphatase 8·5 K.A. units (normal < 3·5), tartrate labile fraction 0·6 K.A. units (normal < 0·8), urine calcium 45 mEq/24 hr on a daily calcium intake of less than 10 mEq, and blood urea 55 mg/100 ml. The phosphate excretion index was + 0·5 (normal ± 0·09) (Nordin and Fraser, 1960). Calcium absorption measured by a double isotope technique was 43% (normal 30-63%) (Reiner *et al.*, 1970). *X*-ray examination showed widespread and florid osteitis fibrosa cystica. A very high bone turnover was shown by a 24-hour calcium-47 space of 54 plasma units (normal < 18) and a mean total urine hydroxyproline of 570 mg/day (range 344-708 mg/day) (normal < 50 mg). A biopsy from a bone cyst in the left pubic bone showed osteitis fibrosa but no malignant cells were seen.

In October 1971 the patient's neck was re-explored by S.T. and the sternum split. Three normal parathyroid glands were found but no tumour tissue. There was no postoperative fall in serum calcium. Palliation of the hypercalcaemia was attempted with a low calcium diet, a high fluid intake, and various more specific treatments. Intramuscular injections of synthetic human calcitonin 0·5 mg three times a day caused a fall in serum calcium towards normal, but it was not sustained for more than 48 hours despite continuous administration for six days and a supplementary infusion of 10 mg over 24 hours. Elemental phosphorus, 2 g daily by mouth, had little or no effect on the serum calcium while intravenous infusions of 1 g of phosphorous element and mithramycin infusions of 2 mg caused only shortlived falls. A single administration of combined cytotoxics consisting of cyclophosphamide (1,000 mg), fluorouracil (750 mg), actinomycin D (0·5 mg), vincristine (2 mg), methotrexate (200 mg), and mithramycin (2 mg) had a shortlived effect similar to that of mithramycin alone. Intramuscular injections of glucagon, 1 mg twice daily for 15 days, did not alter the serum calcium. Venous catheterization of the neck and inferior vena cava was done, and the highest values of parathyroid hormone measured by immunoradiometric assay were found in the right innominate vein at the base of the neck (9·3 ng/ml).

The patient's neck was re-explored on 14 December, but no tumour tissue was found. There was no fall in serum calcium, the patient remained critically ill, suffering intensely from generalized bone pains.

STILBOESTROL DIPHOSPHATE THERAPY

Starting on 21 December, daily injections of stilboestrol diphosphate 1,000 mg were given intravenously for four days. During the first intravenous injection the patient felt extreme and general-

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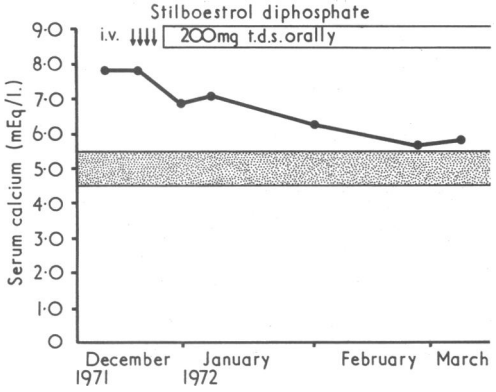
ized bone pain. Treatment was continued by oral therapy 200 mg three times a day and also the low calcium diet and high fluid intake. The serum calcium gradually fell during the next two months to 5·8 mEq/1. (see chart). There was a pronounced general improvement and much less bone pain. He regained his appetite, gained 4 kg in weight, and returned home to become freely



Effect of stilboestrol diphosphate 1 g daily given intravenously for four days, followed by 200 mg three times a day by mouth on serum calcium.

ambulant. Slight, painless bilateral gynaecomastia and occasionally some fluid retention occurred. In March 1972 the peripheral parathyroid hormone level was 7 ng/ml (normal < 1·2 ng/ml) (O'Riordan *et al.*, 1972). A nine-day chromium-corrected calcium balance showed that on a calcium intake of 6 mEq/day the balance was -25 mEq/day. The urine calcium had fallen to 12·5 mEq/day. The phosphate excretion index was +0·41. Radiocalcium absorption from the gut remained as before (37%). No substantial changes were observed in serum inorganic phosphate, blood urea, serum alkaline, and acid phosphatase. The 24-hour calcium-47 space had fallen somewhat to 43 plasma units, and the mean total urine hydroxyproline output was 340 mg/day (range 209-416 mg/day). The bone lesions had neither progressed nor improved.

By the end of March serum calcium had risen to 7 mEq/1. A further course of four daily injections of 1 g of stilboestrol diphosphate was again followed by relief of hypercalcaemia and its symptoms. After seven months on this therapy he was well and the serum calcium was below 6 mEq/1.

Comment

All the drugs available for the long-term management of hypercalcaemia due to inoperable primary hyperparathyroidism failed in the patient except stilboestrol diphosphate, which we believe has not been used before for this purpose. We decided to try oestrogen therapy because we had noted that oestrogens caused a fall in bone turnover in acromegaly, another high-turnover bone disease. Also bone tissue culture studies have shown a direct action of oestrogen in inhibiting bone resorption (Nordin *et al.*, 1970). Furthermore, Goepfert *et al.* (1966) reported a temporary response in a patient with parathyroid carcinoma treated with hexoestrol. Stilboestrol diphosphate is activated in tissues rich in acid and alkaline phosphate, which hydrolyse the phosphate groups and liberate free stilboestrol (Brandes and Browne, 1955). The present patient had high serum acid and alkaline phosphatase (of bone origin), so it seemed that the highest concentrations of oestrogenic hormone in the bones would be achieved by this particular compound.

The mechanism of the hypocalcaemic effect in the patient is uncertain, but the progressive fall in serum calcium in the presence of a high level of parathyroid hormone and unchanged phosphate excretion index suggests that it was not an antitumour effect, as Goepfert *et al.* (1966) claimed in their patient treated with hexoestrol. The reduction in bone turnover suggests an inhibition of bone resorption. The generalized bone pains during the intravenous injections also implies a direct effect of the drug on the bones. The hypocalcaemic effect was not due to increased calcium clearance as urine calcium fell simultaneously with serum calcium, and since the patient was on a very low calcium diet before as well as during the treatment an effect on the calcium absorption could not have been a major factor. It cannot have been due to the slight fall in plasma protein which was observed (0·5 g/100 ml); we corrected the serum calcium values for this change (Dent, 1962). We therefore conclude that the calcium-lowering effect of stilboestrol diphosphate in the patient was probably by a direct inhibition of bone resorption. This is supported by a recent study by Gallagher and Nordin (1972).

Stilboestrol diphosphate would seem to be worthy of further trial in hypercalcaemia due to inoperable parathyroid carcinoma.

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