

1,25-(OH)<sub>2</sub>D<sub>3</sub> treatment, bone and muscle symptoms being particularly improved and the volume proportion of osteoid tissue visible on bone biopsy reduced. Plasma biochemical values and intestinal calcium and phosphorus absorption were either normal or only slightly disturbed at the start of the study; treatment resulted in only mild improvement of the plasma calcium values. Phosphate depletion might have contributed to the osteomalacia seen in these patients, but subnormal plasma phosphorus values would be expected if it was a major factor. The lack of improvement in calcium and phosphorus absorption after 1,25-(OH)<sub>2</sub>D<sub>3</sub> may have been due to the timing of the test: one month after the previous injection, the 1,25-(OH)<sub>2</sub>D<sub>3</sub> may have been largely excreted. The post-treatment fall in urinary calcium excretion might have been caused by greater bone utilisation of calcium. In view of the initial normality and the minimal change in plasma biochemical values after treatment, the effects on bone and muscle might be attributed to a direct effect of 1,25-(OH)<sub>2</sub>D<sub>3</sub>; alternatively, the rise in circulating plasma calcium might have improved bone calcification.

In chronic renal failure the physiological long-term replacement dose of 1,25-(OH)<sub>2</sub>D<sub>3</sub> is about 0.5-1.0 µg/day by mouth; this has resulted in resolution of osteomalacia and secondary hyperparathyroidism.<sup>17</sup> We gave 1,25-(OH)<sub>2</sub>D<sub>3</sub> parenterally in a depot preparation of arachis oil because vitamin D malabsorption occurs in chronic cholestatic liver disease.<sup>3</sup> The half life of 1,25-(OH)<sub>2</sub>D<sub>3</sub> has been calculated as 1½ days<sup>14</sup> but this should be prolonged by the use of a depot preparation. A 1,25-(OH)<sub>2</sub>D<sub>3</sub> assay was not available to us, but after intramuscular injection there is probably a period of rapid release followed by a long period of slow release. A dose of 30 µg 1,25-(OH)<sub>2</sub>D<sub>3</sub> resulted in transient hypercalcaemia. A dose of 15 µg caused no side effects, and the deaths of the two patients were attributed to their terminal liver disease.

The exact nature of the defect(s) of vitamin D metabolism in chronic liver disease remains unknown. Serum 25-OHD values are low in untreated liver disease,<sup>11</sup> but if enough substrate of vitamin D is provided serum 25-OHD concentrations become normal.<sup>6</sup> In our experience, osteomalacia occurs despite normal serum 25-OHD values<sup>2</sup>; the fall in 25-OHD values in our patients and improved histological appearances of bone suggest that 25-OHD is not of first importance in bone mineralisation. 1-Hydroxylation may fail in biliary cirrhosis as in renal disease; this, however, seems to have been relatively unlikely in our patients as renal excretory function was normal. Alternatively, vitamin D<sub>2</sub> metabolites may be less effective in healing hepatic osteomalacia than vitamin D<sub>3</sub> metabolites. This has been previously described in animals.<sup>19</sup> In one series oral 25-OHD stabilised or improved bone mineral content in six or seven patients with PBC, but the underlying bone disease was unknown as histological examination of bone was not performed<sup>20</sup>; the authors did not state whether the 25-OHD originated from vitamin D<sub>2</sub> or D<sub>3</sub>. A subsequent abstract from the same group has

shown reduction in osteoid tissue in six patients with PBC treated with the same metabolite.<sup>21</sup>

Our study shows that the histological osteomalacia of chronic cholestatic liver disease is dependent on defective metabolism of vitamin D. Further research is required to elucidate the nature of defect(s) and the best metabolite and dose to prevent and correct hepatic osteomalacia. If the response to treatment in these four patients was due to a differential response to vitamin D<sub>3</sub> and D<sub>2</sub> metabolites, hepatic osteomalacia might be prevented and healed with vitamin D<sub>3</sub>; if, alternatively, there was a failure of 1-hydroxylation, then 1,25-(OH)<sub>2</sub>D<sub>3</sub> would be the treatment of choice. The mechanism of the "healing" response to 1,25-(OH)<sub>2</sub>D<sub>3</sub> in this study was not apparent in view of the minimal change in measured biochemical variables—various factors may have been playing a part. Nevertheless, vitamin D metabolites may have a direct beneficial effect on bone and muscle in hepatic osteomalacia.

We thank Dr N T Pollitt of Roche Products Ltd, Welwyn Garden City, for providing the 1,25-(OH)<sub>2</sub>D<sub>3</sub>; Miss L Goodwill for preparing the 1,25-(OH)<sub>2</sub>D<sub>3</sub> for parenteral use; Mr S Newman for performing the <sup>47</sup>Ca absorption tests; Dr J M Zanelli for advice; and the National Institute of Biological Standards and Control for providing reagents for radioimmunoassay of immunoreactive PTH. We thank Mr A Chester Beatty for the financial support of RL and the Medical Research Council for the financial support of EM.

Requests for reprints should be addressed to Professor Sherlock, Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG.

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(Accepted 21 October 1977)

## SIDE EFFECTS OF DRUGS

### Tardive dyskinesia associated with metoclopramide

Metoclopramide is widely used for relief of upper gastrointestinal symptoms such as heartburn, nausea, and vomiting. Adverse reactions are relatively rare,<sup>1</sup> but may include disturbances of the central nervous system such as drowsiness, restlessness, and dizziness.<sup>1</sup> Recently acute facial dyskinesias<sup>2</sup> and dystonia<sup>3-4</sup> have been reported in several children and young adults shortly after administration of low doses of metoclopramide. These extrapyramidal effects were attributed to idiosyncrasy, and completely subsided in all cases after withdrawal of the drug. We report on a patient who developed tardive dyskinesia

after long-term treatment with high doses of metoclopramide. We know of no other report of such an association.

#### Case report

A 48-year-old Jewish man began to complain of persistent nausea without vomiting or other gastrointestinal symptoms. No organic basis was found for his complaint, and results of physical and neurological examinations as well as various laboratory tests were normal. There was no evidence of other disease or metabolic abnormalities. There was no history of food or drug allergies in the patient or in his family. Metoclopramide (Pramin, Rafa Laboratories, Israel) was prescribed for the nausea. He took the drug by mouth at a daily dose of 20-40 mg for about six years. He asked for the dosage to be gradually increased, and during the last four years he con-

sistently ingested eight tablets (80 mg) daily without any side effects. Because he could not get metoclopramide without prescription while his regular doctor was away, he abruptly stopped taking the drug.

Ten days later he progressively developed severe persistent facial dyskinesia consisting of repetitive involuntary movements of the lips, jaws, cheeks, and tongue. The latter were mainly constant, forceful sucking, chewing, grimacing, and rapid protrusions of the tongue. Results of general physical and neurological examinations were otherwise normal. Blood count, sedimentation rate, and biochemical and serological examinations showed nothing abnormal. The patient had never received other drugs known to be associated with involuntary movements, such as phenothiazines or butyrophenones. Readministration of metoclopramide at a daily dose of 30 mg resulted in almost complete disappearance of the involuntary movements. Another attempt to withdraw the drug was associated with recurrence of the dyskinesia, which subsided when metoclopramide was given again.

### Comment

The severe involuntary movements developed by this patient after chronic use of high doses of metoclopramide are identical to the syndrome of tardive dyskinesia. The latter is commonly reported in psychiatric patients after long-term administration of phenothiazines or butyrophenones, particularly when these agents are abruptly withdrawn or their dosage reduced.<sup>5</sup> Similarly, our patient developed this extrapyramidal syndrome after long-term ingestion of metoclopramide and sudden discontinuation. Phenothiazines and butyrophenones are potent dopamine-receptor antagonists, and tardive dyskinesia may be caused by a hypersensitivity of central dopamine receptors induced by neuroleptics.<sup>6</sup> Metoclopramide may block cerebral dopamine receptors,<sup>7</sup> and a similar mechanism may have operated in our patient. Paradoxically, tardive dyskinesia sometimes improves after readministration of neuroleptics.<sup>5, 6</sup> Similarly, the involuntary movements in our patient also subsided after reinstatement of metoclopramide. This report should alert doctors to the risk that patients may develop serious and potentially irreversible extrapyramidal side effects after long-term use of metoclopramide.

<sup>1</sup> Pinder, R M, *et al*, *Drugs*, 1976, **12**, 81.

<sup>2</sup> Melmed, S, and Bank, H, *British Medical Journal*, 1975, **1**, 331.

<sup>3</sup> Van Daele, M C, *Archives of Disease in Childhood*, 1970, **45**, 130.

<sup>4</sup> Cochlin, D L, *British Journal of Clinical Practice*, 1974, **28**, 201.

<sup>5</sup> Crane, G E, *American Journal of Psychiatry*, 1972, **129**, 446.

<sup>6</sup> Klawans, H L, *American Journal of Psychiatry*, 1973, **130**, 82.

<sup>7</sup> Dolphin, A, *Psychopharmacology*, 1975, **41**, 133.

(Accepted 18 October 1977)

Departments of Neurology and Internal Medicine A, Hadassah University Hospital and Hadassah Medical School, Hebrew University, Jerusalem, Israel

S LAVY, MD, professor of neurology

E MELAMED, MD, lecturer in neurology

S PENCHAS, MD, lecturer in internal medicine

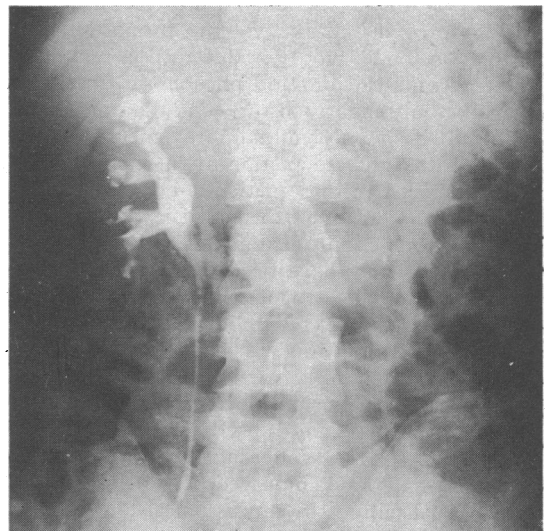
## Dapsone and renal papillary necrosis

This paper records a case of renal papillary necrosis in a patient with dermatitis herpetiformis treated for many years with dapsone in high dosage. Dapsone, which resembles phenacetin in its effect on red blood cells, was probably responsible for the renal disease.

### Case report

A 51-year-old machine assembly supervisor had had attacks of rheumatic fever while in his teens and developed dermatitis herpetiformis in 1957, for which he took dapsone 100 mg three times a day for the first five years, decreasing to 100-200 mg daily more or less continuously without specialist supervision. In 1966 he presented with attacks of acute gouty arthritis, which were treated initially with various drugs and then completely controlled with allopurinol 100 mg thrice daily. During 1972-7 he had about six attacks of renal colic, during one of which he passed some debris.

He first presented at this hospital in March 1977 with an attack of renal colic. Repeated questioning elicited nothing to suggest analgesic abuse. Examination showed a tall, thin (height 188 cm, weight 61 kg), clinically anaemic man with the rash of dermatitis herpetiformis (DH). Blood pressure was 130/80 mm Hg. There were signs of well compensated mitral and aortic



Retrograde pyelogram showing papillary necrosis.

valvular heart disease. Changes of bilateral renal papillary necrosis were seen on intravenous pyelography and confirmed by retrograde pyelography, which was carried out (Dr P M Bretland) to exclude possible ureteric obstruction (see figure).

Results of investigations were as follows: haemoglobin 10.6 g/dl; reticulocytes 6%, occasional fragmented cells and spherocytes; urinary haemosiderin absent; glucose-6-phosphate dehydrogenase screen normal; serum creatinine 180  $\mu$ mol/l (2.0 mg/100 ml); creatinine clearance 35 ml/min; plasma urea 10.5 mmol/l (63.3 mg/100 ml); serum urate 0.27 mmol/l (4.5 mg/100 ml). Glycosuria was not detected, and several random blood glucose measurements were normal.

Skin biopsy with immunofluorescence confirmed the diagnosis of DH (Dr C M Ridley). Circulating immune complexes containing IgG were found (Dr J F Mowbray). There was biochemical evidence of small-bowel malabsorption, and jejunal biopsy showed subtotal villous atrophy.

The patient was treated with a gluten-free diet and only topical applications for the DH.

### Comment

There is no recognised association between papillary necrosis and either DH or its treatment with dapsone<sup>1</sup> and no published evidence incriminating gout or allopurinol. Over the years, however, this patient ingested an estimated 1.25 kg of dapsone, which is more than is normally taken in either DH or leprosy. Like phenacetin, the most likely cause of analgesic nephropathy, dapsone induces a chronic haemolytic anaemia often associated with Heinz body formation.<sup>2</sup> This patient's anaemia was at least partly haemolytic—a condition often found in patients with analgesic nephropathy<sup>3</sup>—and hence the unusually large dapsone intake probably caused the renal damage.

The mechanism by which phenacetin in analgesic mixtures produces renal disease is uncertain. Papillary necrosis is probably the primary lesion but whether the major effect is on the blood supply or due to direct toxicity is controversial.<sup>4</sup> A recent review<sup>5</sup> suggests that vascular mechanisms are the more likely. The papillary necrosis of sickle-cell disease and trait is generally attributed to local ischaemia due to increased blood viscosity. By analogy, this case suggests that alteration in the mechanical properties of red cells may play a part in analgesic- and dapsone-induced papillary necrosis. This tentative hypothesis lends itself to experimental study.

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<sup>3</sup> Murray, R M, Lawson, D H, and Linton, A L, *British Medical Journal*, 1971, **1**, 479.

<sup>4</sup> Heptinstall, R H, *Pathology of the Kidney*, 2nd edn, p 265. Boston, Little, Brown and Co, 1974.

<sup>5</sup> Curtis, J R, *British Medical Journal*, 1977, **2**, 375.

(Accepted 18 October 1977)

Whittington Hospital, London N19 5NF

B I HOFFBRAND, DM, FRCP, consultant physician