therefore result from defective transport of HVA owing to the raised free tryptophan levels rather than to abnormal brain dopamine metabolism. Investigations on brain tissue are required to decide this question.

We had hoped that this study would elucidate the arousal effect of levodopa seen in hepatic coma. The results have shown that this cannot be attributed to defective brain dopamine synthesis, but whether it is due to the flushing away of false neurotransmitters accumulating in the brain in liver failure requires further study (Fischer and Baldessarini, 1971). Conceivably the raised plasma free tryptophan levels are important in the mechanism of the cerebral impairment in hepatic encephalopathy in view of the reported toxic effects of tryptophan in the presence of defective liver function.

We are indebted to the Medical Research Council for its support, to the Laboratories Logeais, Issy-les-Moulineux, Paris, for a research fellowship to A.J.K., and to the National Fund for Research into Crippling Disease for supporting D.B.K.

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MEDICAL MEMORANDA

Osteomalacia due to Phosphate Depletion from Excessive Aluminium Hydroxide Ingestion

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British Medical Journal, 1974, **1**, 551–552

The theoretical dangers of severe phosphate depletion have been known for a long time. Minor degrees might be expected first to affect bone mineralization and then to produce a disease similar to rickets (or osteomalacia) while severe depletion would lead to death. Aluminium hydroxide is nearly always given as an antacid. Rarely, as in certain patients with renal failure, it is given in larger doses to produce a slight phosphate depletion, for the hydroxide not neutralized by the gastric acidity (and probably most that is) is likely to bind with the phosphate in the diet and intestinal secretions and be excreted unabsorbed as aluminium phosphate. With the usual doses given severe phosphate depletion should not occur but with larger doses it would seem to be inevitable. We describe such a case here.

Case Report

A housewife aged 49 years was admitted in April 1973 complaining of pain in the left hip and of weakness and difficulty in walking over a period of five months. The pain had begun suddenly for no apparent reason, had later become severe, and was made worse by rising from a sitting position and climbing stairs. More recently she had felt pain in both upper arms and in the lower lumbar region. Weakness was most noticeable when she tried to rise from a sitting position. Her gait had been described by friends as waddling, and on admission she was able to walk a few paces only with great difficulty. The results of previous investigations had been normal, but later abnormalities in plasma calcium, phosphorus, and alkaline phosphatase led to her referral to this unit.

She had a history of severe heartburn, associated with reflux oesophagitis and hiatus hernia, which antacids relieved. Her appetite was normal but she had eaten sparingly for two years, avoiding all starchy foods and alcohol, and had lost 12 kg in weight. There were no other symptoms. She had had a hysterectomy for menorrhagia in 1971. Since January 1971 her antacid intake had consisted of 500-600 ml Aludrox a week, equivalent to about 4·7 g aluminium hydroxide daily. This was discontinued after nine months in favour of Mucaine at least 10 ml hourly, equivalent to about 11·4 g aluminium hydroxide, 4·0 g magnesium hydroxide, and 400 mg oxathazaine daily. In addition she had taken 15-20 Asilone tablets daily for the last 20 months, equivalent to about 8·5 g aluminium hydroxide and 4·2 g polymethylsiloxane daily. Thus for some months before admission she had taken about 20 g of aluminium hydroxide each day—far in excess of the normal therapeutic dose. She had also taken nightly nitrazepam 5 mg, levorphanol tartrate 3 mg, and two tablets each of Tuinal and Equagesic.

The patient was small and thin (weight 51·0 kg, height 152·2 cm), but looked in good general health. She had a pronounced waddling gait and weakness of the hip and knee flexors. Passive joint movement was normal. There was tenderness around both humeri and the left hip but no generalized bone tenderness and no weakness of the shoulder muscles. Preliminary investigations showed normal haematology, normal urea, sodium, potassium, chlorine, uric acid, and creatinine, with a creatinine clearance of 80 ml/min. The plasma immunoreactive parathyroid hormone level was 1,075 pg/ml (normal up to 650 pg/ml), and the plasma 25-hydroxyvitamin D on three occasions was 13, 14, and 16 ng/ml respectively (normal 7-23 ng/ml for April; T. C. B. Stamp, personal communication). The results of routine urine examination were normal. Skeletal radiological screening showed nothing abnormal; in particular there were no Looser zones or subperiosteal erosions. Using copper thiocyanate as internal marker we found faecal fat to be raised on the first determination at

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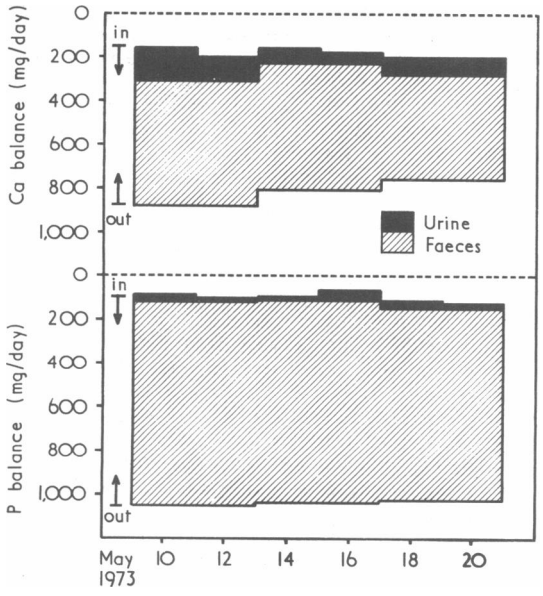
Relevant Biochemical Findings in Patient with Phosphate Depletion after Taking Aluminium Hydroxide

			Fasting Plasma Levels (9 a.m.)			Urinary Excretion Levels		
			Calcium (mg/100 ml)*	Phosphorus (mg/100 ml)	Alk. Phosphatase (K.A. Units)	Calcium (mg/24 hr)	Phosphorus (mg/24 hr)	Total Hydroxyproline (mg/24 hr)
Outpatient		25 April	9·6	0·8	24	906	<14	69
Inpatient	Self-chosen diet	30 April	9·6	1·2	23	665	20	58
		3 May	9·7	2·4	—	422	2	51
	Constant balance diet	7 May	9·3	2·8	23	299	3	70
		10 May	9·3	3·0	22	146	14	68
		14 May	9·0	3·0	20	64	25	93
		17 May	9·3	3·2	19	67	28	107
		21 May	9·1	3·0	20	73	8	103
	Self-chosen diet	25 May	8·4	4·7	23	28	903	159
Outpatient		12 June	8·9	2·9	20	36	341	—
Outpatient		13 August	9·0	2·9	14	83	166	—

*Corrected for specific gravity.

8·2 g/day but in two later collections taken during four-day balances (see below) it had fallen to 2·7 and 2·9 g/day. Relevant fasting plasma levels on 25 and 30 April respectively were as follows: calcium, corrected for specific gravity (Dent *et al.*, 1961), 9·6 and 9·6 mg/100 ml; phosphorus 0·8 and 1·2 mg/100 ml; alkaline phosphatase 24 and 23 K.A. units (see table). Corresponding urinary excretion rates were: calcium 906 and 665 mg/24 hr, phosphorus <14 and 20 mg/24 hr. The daily diet had contained about 48 g protein, 84 g carbohydrate, 60 g fat, 433 mg calcium, and 633 mg phosphorus. A dietary vitamin D intake of only about 4 IU/day had been supplemented by a daily capsule containing 600 IU vitamin D.

At first the previous self-chosen diet and high Mucaine intake was continued and the patient told to take as much Asilone as she felt she needed. As soon as possible collections were obtained for three four-day calcium and phosphorus balances performed in the usual way with internal faecal marking with copper thiocyanate. While running up for the balance the 24-hour urinary excretion of calcium began to fall and the plasma phosphorus to rise (see table). The patient had taken no Asilone and her aluminium hydroxide intake had fallen to about 8 g/day. She was kept on this lower intake and began to improve clinically as a result. The balance results (see diagram) later showed she was in positive balance for both calcium and phosphorus in the correct proportions (2:1) for bone formation, thus confirming that her bones were healing. The 24-hour urinary calcium excretion fell during the balance, but the high faecal phosphorus and low urinary phosphorus excretion remained grossly abnormal. After the balance the aluminium hydroxide (Mucaine) was slowly decreased to about 100 ml daily and a daily supplement of 5 g disodium hydrogen phosphate was given for four days. The plasma phosphorus rose to 3·2 mg/100 ml but the urinary output of phosphorus remained very low, thus confirming that a renal phosphorus leak was not a contributory cause of the osteomalacia. The patient left hospital greatly improved on 23 May. She continued to take moderate doses of calcium carbonate and of its mixture with glycine (Titralac), and she returned to small doses of Mucaire. Three months later she was walking normally and painlessly. The result of a bone biopsy in April had confirmed the origina l diagnosis of osteomalacia.



Calcium and phosphorus balances in patient taking reduced dose of about 8 g daily aluminium hydroxide, showing positive balance in ratio of Ca:P=2:1.

Comment

After some months of other investigations the difficult clinical picture in this patient was correctly interpreted only by routine plasma screening, and the diagnosis of phosphate deficiency was confirmed by the eventual cure of the disease by merely withholding aluminium hydroxide. We know of only three other detailed studies (Bloom *et al.*, 1960; Lotz *et al.*, 1964, and 1968) of phosphate depletion caused by taking aluminium hydroxide either in normal volunteers or in patients with osteomalacia. Patients taking aluminium hydroxide, especially those with renal failure (Dent *et al.*, 1961), should be closely watched at least for milder manifestations of the disease than we have reported here. The clinical signs in a mild case would be rather vague, comprising only generalized, poorly localized pains and muscle weakness. The biochemical signs, however, would be characteristic—a low plasma phosphorus, perhaps raised alkaline phosphatase, and a high calcium and low phosphorus urinary content. No other form of metabolic osteomalacia—there are over 30 forms known now (Dent, 1971)—shows this particular combination of abnormalities.

We thank the nurses, dietitian, and biochemists on the metabolic ward for their essential services. The patient was kindly referred by Dr. N. Halper, who drew our attention at the time to the patient's high intake of aluminium hydroxide. Dr. P. E. Jones gave valuable assistance in meeting the editor's requirements for brevity.

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