index case had been admitted to the hospital. Case 5 had the first signs of a *Y. enterocolitica* infection about 14 days after she came to work in ward A, where three other people with the disease were working. This evidence indicates a common chain of infection, starting with case 1.

The fact that so many persons contracted the disease indicates the high infectivity of *Y. enterocolitica*. The incubation time would appear to be about 10 days. No other patients are reported as having the infection, but since the disease was generally mild and the diagnosis of most of the staff members was established about 2 weeks after the first case had occurred, some cases may have passed unnoticed. Familial infections,[1,2,4–8,12] and even small outbreaks [8,13] have been reported. In these cases, however, a common source of infection has been suspected rather than spread from person to person. From our observations it seems that the infection can be spread from person to person directly. Infection was probably spread when the patient with diarrhœa soiled her bed, but the possible infection of case 5 by three other nurses and the probable occurrence of *Y. enterocolitica* infection in the families of cases 3 and 7 are more difficult to explain. However, the risk of contamination may be even higher and more insidious than usual when the staff are dealing with patients having abdominal pain as their main symptom (as our case 1), especially if *Y. enterocolitica* infection is not suspected. Factors contributing to the high infectivity of *Y. enterocolitica* include its ability to grow at room temperature [4] and to survive in tap-water.[14]

The main symptoms in all cases we have described were abdominal pain and diarrhœa. Four patients had fever, and four had joint symptoms, none of these symptoms were severe, but in two cases they lasted for over 5 months. At least two patients had abdominal symptoms which were not severe enough to warrant medical attention had the staff not been aware of the diagnoses in the other cases. The clinical features of *Y. enterocolitica* infection in all our cases accord well with those described earlier.[1–8] Quite severe infections with carditis and septicæmia have also been described.[6–8]

As a result of improved diagnostic methods, *Y. enterocolitica* infection can now be regarded as quite common in many countries.[3,4,7,8,12,13] The specific diagnosis requires stool bacteriological cultures in the early phase, and/or antibody titrations. Unless the possibility of *Y. enterocolitica* infection is considered, the symptoms may easily be overlooked or misinterpreted. It is not unlikely that some cases diagnosed, for instance, as rheumatoid arthritis, suspected appendicitis, or gynæcological disorders are really *Y. enterocolitica* infections.

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MAGNESIUM-INDUCED REVERSAL OF VITAMIN-D RESISTANCE IN HYPOPARATHYROIDISM

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Summary A 13-year-old girl had hypoparathyroidism which was refractory to therapy with high doses of vitamin D_2 (given orally and intramuscularly), dihydrotachysterol ('A.T. 10') treatment, and up to 8 g. per day of calcium-salt supplement. The patient responded convincingly when 25 meq. of magnesium per day was given in addition to moderate oral doses of vitamin D_2.

Introduction

SINCE the early description of Blohm et al.[1] there have been several reports of resistance to vitamin-D therapy in the treatment of idiopathic or post-surgical hypoparathyroidism.[2,3] In some patients the substitution of dihydrotachysterol ('A.T. 10') for calciferol has been beneficial.[2] However, when calciferol and dihydrotachysterol are not effective, hypocalcæmia can lead to persistent tetany and to intractable convulsions.

We report a patient with idiopathic hypoparathyroidism and severe symptomatic hypocalcæmia who did not respond to treatment with vitamin D_2, dihydrotachysterol, and very large oral supplements of calcium salts. However, she responded when oral supplements of magnesium were given.

Case-report

The patient was first seen at the age of 13 years. She had been born after an uneventful full-term pregnancy and normal vaginal delivery. The only important feature of her history was an attack of acute rheumatic fever at the age of 11 years. At the age of 12·5 years the parents noted changes in the child's behaviour, and she had brief attacks of unconsciousness, accompanied by occasional muscular twitchings.

There were electroencephalogram changes suggestive of petit mal, and she was treated by a neurologist with phenytoin and phenobarbitone. However, there was no improvement and she was admitted to hospital for investigation.

Physical examination revealed a normally developed and

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intelligent child. There were no abnormalities of the skin, hair, or nails. External genitalia and secondary sex characteristics were normal for her age, and she menstruated for the first time while in the hospital. Her blood-pressure was 105/45, her pulse was 78 per minute and a neurological examination revealed nothing abnormal, except for unequivocally positive Chvostek and Trousseau signs. Laboratory data are summarised below:

Substance	*Level*
Serum-calcium	5·1–6·8 mg./100 ml.
Serum-phosphorus	9·8–10·1 mg./100 ml.
Serum-glucose	72–90 mg./100 ml.
Total serum-proteins	7·0–8·0 g./100 ml.
Serum-albumin	3·8–5·0 g./100 ml.
Serum-globulin	3·0–3·2 g./100 ml.
Serum-cholesterol	160–180 mg./100 ml.
Blood-urea-nitrogen	10–16 mg./100 ml.
Serum-alkaline-phosphatase	2·0–2·1 Bessey-Lowry units
Serum-sodium	142–145 meq./l.
Serum-potassium	3·8–4·1 meq./l.
Serum-chloride	98–103 meq./l.
Creatinine clearance	Normal
Serum-cortisol	20·3–21·9 µg./100 ml.
Urinary 17-ketosteroids	4·2 mg./day

The electrocardiogram showed persistent QT-segment prolongation, reflecting the profound hypocalcæmia. A clinical diagnosis of idiopathic hypoparathyroidism was made. Responsiveness to exogenous parathormone was investigated by administration of parathyroid extract (200 units of ' Paroidin ', Parke-Davis), and this produced a significant phosphorus diuresis (fig. 1).

Treatment with oral calciferol in progressively increasing doses (up to 250,000 units per day) plus 3 to 4 g. of calcium-lactate supplement had no effect on serum-calcium concentration. Thus, in February, 1970, vitamin D_2 was administered intramuscularly in doses which increased progressively up to 600,000 units daily. After 13 weeks of intensive therapy, calcium levels were between 6·0 and 6·6 mg. per 100 ml. and phosphorus levels were between 9·1 and 10·0 mg. per 100 ml. Therapy with dihydrotachysterol (0·625–1·875 mg. per day) plus 4 g. of calcium lactate and 4 g. of calcium chloride did not produce any clinical or biochemical response. The serum-magnesium at that time was 0·6 mg. per 100 ml. In March, 1971, the patient had a convulsion and was admitted with severe generalised tetany. She was given 1·5 g. of calcium gluconate intravenously, and was subsequently treated with 1·2 million units of vitamin D_2 and 4 g. each of calcium lactate and calcium chloride. Over the next month there was no clinical change and calcium levels remained low.

In May, 1971, at the suggestion of Dr J. E. Howard and Dr T. J. Connor, 25 meq. of magnesium was administered orally as a mixture of magnesium citrate and chloride, together with 300,000–500,000 units of oral vitamin D_2. She improved quickly and after 6 weeks the serum-calcium had risen to 8·0 mg. per 100 ml. In August, 1971, vitamin D_2 and oral calcium supplements were stopped because of symptom-free hypercalcæmia of 12·3 mg. per 100 ml. Treatment was restarted one month later with 100,000–200,000 units per day of vitamin D_2 and 25 meq. of magnesium. Her calcium levels have remained stable between

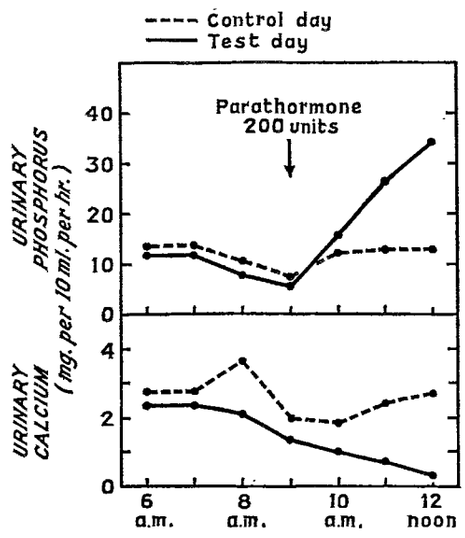

Fig. 1—Response of urinary calcium and phosphorus to intramuscular injections of normal saline (control) and 200 units of parathormone.

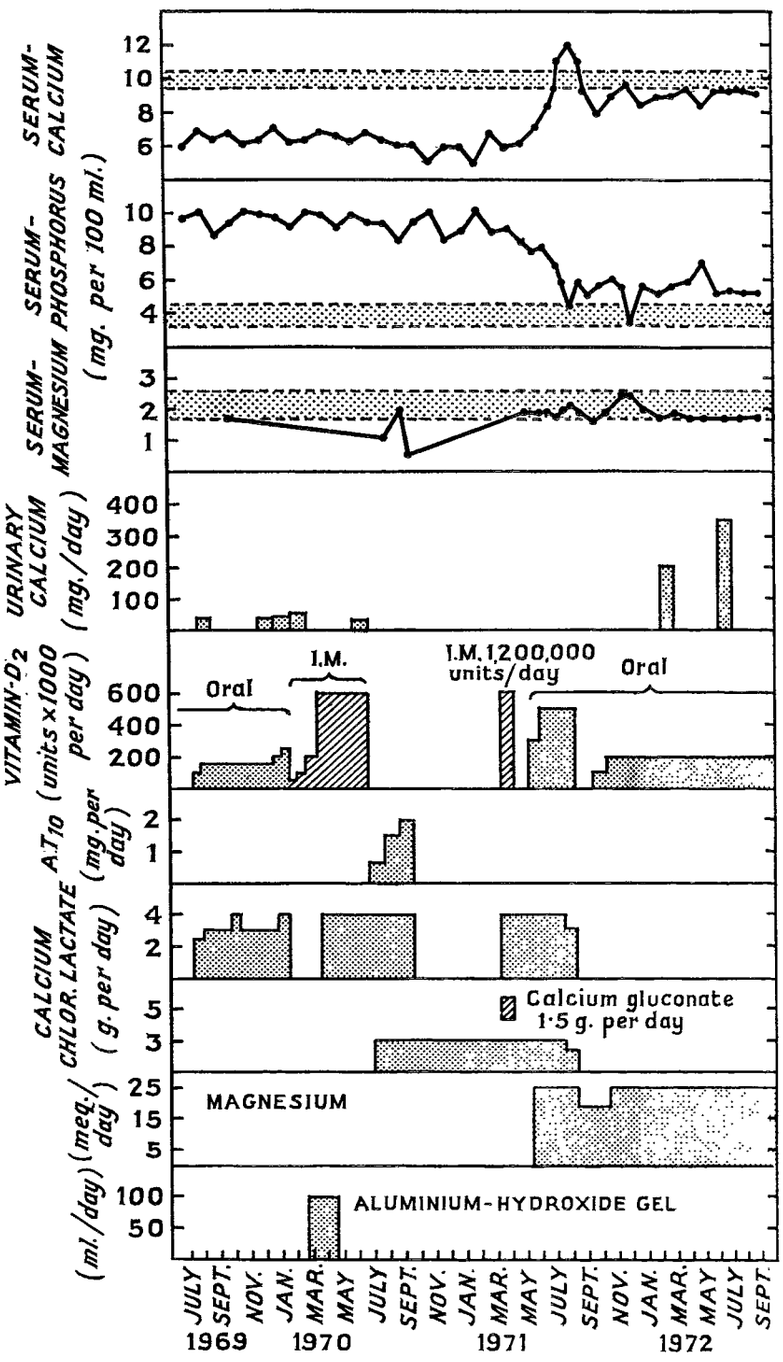

Fig. 2—Changes in serum calcium, phosphorus, and magnesium and urinary calcium in response to different therapeutic regimens.

I.M. = Intramuscularly.

8·0–9·5 mg. per 100 ml. and phosphorus levels have stabilised at 3·6–6·6 mg. per 100 ml. Chvostek and Trousseau signs have disappeared and she has been well and completely symptom-free on this therapy.

Discussion

Our patient presented a difficult therapeutic problem. Hypocalcæmia was refractory to vitamin D_2, administered intramuscularly in concentration of up to 1·2 million units daily; neither did dihydrotachysterol and up to 8 g. of oral calcium-salt supplements produce any response. There was a positive biochemical and clinical response to oral doses of 100,000–200,000 units of vitamin D_2 after starting oral magnesium supplements (fig. 2).

Several workers [4–6] have described the usefulness of magnesium supplements in vitamin-D-resistant hypoparathyroidism. Homer's case [4] was resistant to massive amounts of medication (8·85 mg. of dihydrotachysterol, 300,000 units of calciferol, and 100 g. of calcium per day). Magnesium sulphate was added, which partially reversed the situation. Yendt et al. described a similar patient who was unable to maintain normocalcæmia with vitamin D_2, dihydrotachysterol, and cortisone given orally and parenterally. Magnesium supplements reversed the insensitivity to the vitamin. His patient, like ours, was sensitive to parathyroid hormone, and this does not accord with the unresponsiveness to parathormone often observed in magnesium-deficient states. Thus Estep et al.[7] noted attenuated calcæmic and phosphaturic effects of parathormone in alcoholic hypocalcæmic hypomagnesæmic patients. Responsiveness was restored by magnesium repletion.

Magnesium levels are often below normal in states of chronic hypoparathyroidism.[6] This appears to be a consequence of reduced gut absorption and excessive urinary loss of magnesium.

Can these observations help us to understand the dramatic change in sensitivity to vitamin D_2 which occurred after magnesium therapy in our patient? 25-hydroxycholecalciferol (25-H.C.C.) is one of the active metabolites of vitamin D_3,[8,9] and is produced by the 25-hydroxylation of vitamin D_3 in the liver. Vitamin-D-resistant hypoparathyroidism has been successfully treated with relatively small doses of 25-H.C.C.[3] Horsting and De Luca [10] have demonstrated that homogenates of rat liver were able to perform the 25-hydroxylation of vitamin D_3 when reduced pyridine nucleotides, magnesium ions, and oxygen were present in the media. Thus 25-hydroxylation may be magnesium dependent. Magnesium depletion often accompanies hypoparathyroidism, and magnesium supplementation may have made possible the formation of the biologically active derivatives of vitamin D.

While the mode of action of magnesium remains unclear, its use should be considered for patients with hypoparathyroidism who are refractory to conventional therapy.

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Hypothesis

ACTION OF BONE HÆMODYNAMICS ON LACUNÆ-WALL CALCIFICATION

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Summary Increase in the venous pressure of a limb produced by venous ligation or by the creation of an arteriovenous fistula accelerates fracture consolidation and bone growth. In contrast, factors which should reduce the bony intramedullary venous pressure, such as paralysis, bed rest, or exposure to zero gravity, tend to decalcify bone or retard its growth. It is suggested that changes in a limb venous pressure produce alterations in bone calcium deposition. An increase in venous pressure should increase capillary filtration. This would cause œdema in most organs. Bone, because of its rigid structure, cannot swell; therefore, excess interstitial fluid production in this organ should produce an increase in interstitial-space pressure. Changes in the pressure of a crystallising solution would alter the rate of crystal formation and dissolution. Therefore, increases in the bony interstitial-space pressure should increase the crystallisation-rate at the lacunæ wall, and lowering the lacunæ pressure by a reduction in limb venous pressure should induce crystal dissolution. This hypothesis will only be valid if all other factors involved in bone metabolism (i.e., hormonal, ionic, &c.) are present and functioning normally.

INTRODUCTION

THE interstitial space in cortical bone encompasses the lacunæ and canaliculi systems.[1] The physiology of the interstitial space is closely related to that of the capillary system, and a study of the anatomy of bone reveals an apparently inadequate venous system [2–4] when compared with the generous venous system of other organs. Long bones have one or two small nutrient veins and several extremely small periosteal venules which would not appear to be able to cope hæmodynamically with a large venous effluent.

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