Treatment of hereditary hypophosphataemic rickets

Sir,

We read with interest the article by Stamp and Baker (*Archives*, 1976, **51**, 360). While the conclusions of the authors with respect to genetics are of much importance, equally so are the therapeutics of this disorder, and here we should like to give our experience with phosphate supplements.

Our results with Phosphate-Sandoz (Sandoz Products, London) compare very favourably with earlier results, both in our own and in other institutions. This phosphate preparation (one tablet contains sodium acid phosphate 68.1%, sodium bicarbonate 9.5%, and potassium bicarbonate 8.5%; providing, in addition to phosphorus 500 mg, sodium 481 mg=20.9 mEq and potassium 123 mg=3.1 mEq) is given in a dose usually of 4-6 tablets per day. This basic medication, usually given for life, is supplemented by vitamin D. The dosage of vitamin D can be kept remarkably low (usually 20 000-60 000 IU/day) thus avoiding the hazards of intoxication. Indeed the sequelae of vitamin D intoxication could have been the cause of some of the clinical findings of the patients described by the authors.

This therapeutic regimen for hereditary hypophosphataemic rickets has proved successful in both biochemical (serum phosphate, alkaline phosphatase, and calcium; urinary calcium) and clinical terms; side effects of the phosphate supplementation such as diarrhoea are only rarely observed.

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Dr. T. C. B. Stamp comments:

Many workers have reported satisfactory long-term control of hypophosphataemic rickets with combinations of vitamin D and a phosphate supplement (West *et al.*, 1964; Stickler, Hayles, and Rosevear, 1965; Wilson *et al.*, 1965; Glorieux *et al.*, 1972; McEnery, Silverman, and West, 1972). The convenient commercial preparation advocated by Dr. Koepf was used by us in one of our cases.

In our experience optimum long-term control of X-linked rickets can be achieved without extra phosphorus (Dent, Round and Stamp, 1973), in contrast to the situation in adult-presenting hypophosphataemic osteomalacia where supplementation seems necessary (Dent and Stamp, 1971). Additional phosphate may also benefit the severe homozygous disease described in our paper, since supplementation in one patient produced an alkaline phosphatase 'flare'.

One of the major problems of therapy in all these diseases is that the only generally available preparations of vitamin D, 'strong calciferol' (BP and USP), contains 50 000 IU in each tablet, a quantity far too large to permit accurate dosage (Dent *et al.*, 1973). These tablets may even contain up to 30% more vitamin D than is

stated (so-called 'overage') in order to allow for slow deterioration on storage. For this reason alone we can look forward to alternative therapy such as 25-hydroxy-cholecalciferol.

Phosphate supplementation in X-linked rickets can certainly reduce the danger of intoxication that is present with such high doses of vitamin D and may also lower the requirement. Its disadvantages are firstly the need to 'juggle' two lots of pills instead of one, secondly the still-present danger of vitamin D intoxication if a patient should stop the supplement for any reason, and finally the increased secondary hyperparathyroidism which phosphate produces (Arnaud, Glorieux, and Scriver, 1971) and to which these patients may be particularly liable.

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Genetic aspects of nutritional rickets

Sir,

In their study Doxiadis *et al.* (*Archives*, 1976, **51**, 83) conclude that '... in at least some cases of nutritional rickets there is a genetic element which may manifest itself only under adverse environmental conditions'. This explains why only some children with nutritional deficiency may develop rickets, and why only some children treated with phenobarbitone may also develop rickets. 162 children on long-term treatment with phenobarbitone (5 mg/kg per day) have been observed as outpatients. In 30% of those aged 0-13 years (average duration of treatment 20 months) and in 60% of patients aged under 2 (average duration of treatment

10 months) there was an increase in serum alkaline phosphatase values. But the incidence of raised alkaline phosphatase values was not found to increase after the 4th month of therapy.

These results are in agreement with the idea that alteration of phosphorus/calcium metabolism during treatment with phenobarbitone depends more on individual sensitivity than on the length of time the drug is given. Phenobarbitone and comparable drugs thus represent 'adverse environmental conditions' capable of making evident the 'genetic defect'.

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Nutritional deprivation during protracted diarrhoea after acute gastroenteritis

Sir,

We have been concerned at the poor nutritional state of a number of infants referred to us in recent years for the management of 'intractable diarrhoea', and would like to comment on one particular aspect of the management of such patients in the earlier stages of their illness.

Persistent diarrhoea after an episode of acute gastroenteritis is a well recognized problem, and most infants with 'intractable diarrhoea' referred to us start their illness in this way. Many are less than 3 months of age at onset. It seems to be common practice in such infants whose loose stools persist after the initial reintroduction of their usual milk formula, to change quite quickly (often before the full strength of the feeding is reached) to another formula which may or may not be significantly different as regards the type of fat, protein, or carbohydrate which it contains. If the stools do not improve then, or the baby fails to gain weight quickly, further formula changes are made. These changes may have relevance to stool investigations suggesting sugar intolerance, or be made on the presumption that cows' milk protein cannot be tolerated, but often they are made because it is simply felt that the child's gut can no longer deal with the normal constituents of unmodified cows' milk. Each new formula is introduced in a diluted form and gradually built up to full strength if possible. This sequence of events usually results in the child's calorie intake being compromised for many days, as he is gradually weaned from one milk to the next.

While we are fully cognizant of the difficulties of managing such infants, we feel that it is not often appreciated just how deficient is the calorie intake over long periods. The ease with which this may happen is exemplified by some details with regard to 2 of the 9 such children who have come under our care this year; these being the 2 from whose previous records we could estimate the nutritional intake with some degree of

accuracy. Both originally presented as cases of acute gastroenteritis. Despite dietary manipulation, loose stools persisted and were not explained by extensive investigations. Some details of their management are shown in the Table.

TABLE

	Case 1	Case 2
Age at onset of illness (d)	69	22
Days in referring hospital	151	37
Days with calorie intake <120 cal/kg per day	94	37
No. of different milk formulae used	8	6
No. of times formula or concentration of formula was changed	46	16
% short-fall of observed-to-expected weight on admission to Birmingham Children's Hospital	56%	50%

The deleterious effect of starvation on gut function is increasingly being recognized (Avery *et al.*, 1968; Gall and Hamilton, 1974) and there is no doubt that once diarrhoea has continued for a period of time, various self-perpetuating mechanisms come into play which tend to make the condition irreversible. Though the initial management of gastroenteritis will vary in different hands, the risks of nutritional deprivation must be constantly borne in mind. If an adequate oral intake is not tolerated within a few days, then attention must be concentrated on the maintenance of fluid balance and the satisfactory provision of nutrients, with perhaps lesser attention to the restoration of the stools to normal number and size within a short period, as emphasized by Fomon, Ziegler, and O'Donnell (1974). A persisting inability to maintain adequate fluid and calorie intake and prevent progressive loss of weight should make peripheral intravenous calorie as well as fluid supplementation mandatory before the nutritional deficit has reached anything like the severity noted in the 2 cases above. The occasional patient will eventually require central venous alimentation; however, we stress the many potential hazards of the latter course of management and suggest that it should only be carried out in units experienced in the techniques.

One of us was a junior doctor a good many years ago, when a consultant expected the daily calorie as well as fluid intake of each sick baby to be known by the houseman and sister. A casual statement that both were adequate was not acceptable. Maybe this is still common practice in many paediatric units, but in almost all the cases referred to us there was no written evidence in the notes of either medical or nursing staff that calorie intake had been calculated during the successive changes of milk formulae and the deficit recognized before gross malnutrition was evident.

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