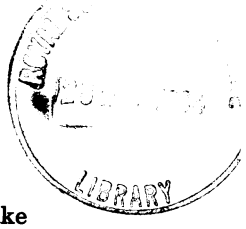
Editorials



'Ring out . . .'

This issue of the *Journal* is the last in its present form. It is also the last under the present editor who welcomes the new editor bringing, in January 1995, his ability and distinction in clinical and academic medicine and considerable experience in matters of medical scientific journals. The pleasure is doubled by the knowledge that the new editor will have a deputy editor, also accomplished in medical journalism, to deal with the publication of material arising from the meetings of the Sections and the Forums, one who by happy chance worked for a period of his surgical training with the present incumbent. So it is with confidence that on retiring he calls upon readers to welcome and support the new team who will enhance the international standing of the *Journal* and the reputation of the Royal Society of Medicine as a great academic home for the profession of Medicine at large. So - 'on our heels . . .'

The retiring editor is resisting the temptation here to escort the reader on a guided tour down his own memory lane of 38 years of medical authorship and editorship. Of the shrines to visit one bears the superscription 'Literacy and Numeracy'[1], and another 'Fire-in-the-Belly', that important requirement of authorship which forces the editor to distinguish between material submitted for the sake of the work and that coming from those motivated to strain and strive to 'weave a paradise for a sect'. Much time would be spent viewing the now mangled silver cord of Hippocrates (oath and canon), the politically tortured and ravished body of Hygeia and what remains of that good and honest, but so often own-goal-rubbished Panacea. On the way we would pass 'through the misty solitudes' where the road is obscured, and by the crumbling haunts of coppersmiths, the abodes of wind-suckers (propriety forbids the Elizabethan spelling) and those pools of refreshing water wherein are writ better deeds and virtues. Yes, an interesting journey of reminiscence, but 'such a long journey' is not needed at this time of rebirth and a new dispensation. Wisely, your retiring editor must be content to present a Christmas collation suitable for all those who enjoy reading about the many splendoured thing that is the practice of Medicine, and in wishing readers a Happy Christmas and a good New Year he continues in elemental and enigmatic mood finally to offer them a choice - between Milton and Tennyson - 'Ring out . . .'.

A J Harding Rains
Editor

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1 Central Advisory Council for Education. *A Report of the Central Advisory Council for Education, England: 15-18.* Vol 1. The Sixth Form. Chap 25, Part 5. London: HMSO, 1959:268 (para 397)

Privational rickets: a modern perspective

In this issue the paper by Gibbs (see pp 729-32) provides a unique historical perspective of the problems of vitamin D deficiency rickets in England until the early twentieth century. Since that time considerable advances have been made in our understanding of the physiology of vitamin D and its metabolites, and of the pathogenesis of the many causes of rickets in children. Despite these advances, privational rickets is still seen in a number of communities not only in the developing world but also in industrialized nations.

In the USA, attention has been drawn recently to the problem of rickets in breast-fed infants of black vegetarian mothers and in infants receiving strictly vegetarian or macrobiotic diets[2-4]. Rickets also remains common in countries where sunshine exposure should not be a problem: e.g., India, Greece, Turkey, Egypt, Saudi Arabia, and among the Bedouin in the Middle East. In the UK, the Asian communities have a high prevalence of the disease[5,6]. It is the investigations into its pathogenesis in this latter group, which have led to a greater understanding of the pathogenesis of privational rickets and have provided us with a unifying concept of possible mechanisms by which rickets in these apparently disparate at-risk groups might be explained[7].

Rickets and osteomalacia are common in both Asian children and adults in England, but are almost never seen in the immigrant black community. A number of risk factors has been associated with the development of the disease; these include high latitude, Hindu religion, immigration from east Africa, vegetarianism, high fibre diets and the consumption of chapatti[5,6,8]. Although all cases are associated with a low vitamin D status, simple sunlight deprivation is unlikely to explain the high prevalence of the disease in the community, as immigrant black people do not have higher sunlight exposure. The degree of melanin pigmentation influences the amount of ultra-violet light penetrating the epidermis. It would therefore be expected that the darker skinned individuals would

be more at risk. However, this does not appear to be the case, as many of the patients suffering from rickets are relatively lightly pigmented.

The association with vegetarianism, high fibre diets, and high extraction cereal consumption suggests that dietary factors play a role. The contribution of the dietary vitamin D intake to the vitamin D status of the British population is minimal as foods are generally not fortified. Although the exclusion of meat (and animal fat), eggs and milk by Asians who are strict lactovegetarians, could contribute to the development of vitamin D deficiency, this alone does not explain the high prevalence of rickets in the community. Thus, the role of other dietary constituents of the vegetarian diet, such as the high fibre content and the consumption of high extraction cereals, must be considered.

Over the past decade, several studies have helped to elucidate the possible role of vegetarian diets in the pathogenesis of vitamin D deficiency. Both high fibre diets and intestinal malabsorption have been shown to reduce the serum half-life of 25-hydroxyvitamin D (25-OHD), the major circulating metabolite of vitamin D, by approximately one-third[9,10]. Studies in rats have clearly demonstrated that an elevation of serum 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D) concentrations increases the metabolic clearance of 25-OHD without altering its production rate[11-13]. These changes could be induced by the administration of 1,25-$(OH)_2$D or by increasing its endogenous production through feeding the animals low calcium or high fibre containing diets. The increase in metabolic clearance rate of 25-OHD could be accounted for by the increase in excretion of more polar metabolites in the faeces. Studies in man have confirmed many of these findings[14], and in long-term studies in which 1,25-$(OH)_2$D was administered to subjects there was a significant correlation between the observed fall in plasma 25-OHD levels and the predicted fall calculated from the change in plasma half-life of ^{3}H-25-OHD, which had been injected to assess the perturbations in metabolic clearance rate.

High phytate or phosphorus containing diets increase parathyroid hormone secretion and 1,25-$(OH_2$D concentrations, probably through the impairment of calcium absorption[15]. Elevation of 1,25-$(OH)_2$D levels increases the catabolism and shortens the half-life of 25-OHD, thus increasing vitamin D requirements. In situations where the vitamin D status of the community is marginal, as, for example, among Asians in the UK, the increased demand for vitamin D is sufficient to precipitate vitamin D deficiency and the development of rickets. Although this hypothesis has not been confirmed, several clinical studies support it. Asian rickets can be prevented or treated by small doses of vitamin D, but more importantly, researchers have reported the healing of rickets by removal of chapatti from the diet[16]. It is apparent, therefore, that the calcium content of the diet and its availability in the intestine for absorption play important roles in determining the metabolic clearance of 25-OHD and thus the vitamin D status, especially in those individuals whose vitamin D supply is marginal.

These data provide a rational explanation for the high prevalence of rickets and osteomalacia among the Asian community in Britain, and for why rickets is still a problem in breast-fed infants of vegetarian mothers in the USA. They might also explain the frequency of rickets among other communities in which high fibre and phytate diets are common, such as the Bedouin in the Middle East.

Privational rickets is generally associated with evidence of vitamin D deficiency (low serum 25-OHD concentrations), however this is not always the case. Rickets has been described in infants with normal serum concentrations of 25-OHD, who were fed diets low in calcium, such as unsupplemented meat or soya bean based liquid diets[17]. Further, rickets and osteomalacia have been reported to occur in rural children (aged 4 to 16 years) in South Africa whose dietary calcium intakes have been estimated to be between 200 and 250 mg/day[18,19]. In these children serum 25-OHD concentrations are normal and 1,25-$(OH)_2$D levels elevated. The diets of these children are typically devoid of dairy products and consist of a staple of maize meal to which is added a stew of onions, green leafy vegetables and tomatoes at the midday and evening meals. Not only is this diet low in calcium but it is also high in phytate and in many cases oxalate. Both of these latter compounds impair calcium availability in the gastrointestinal tract, thus further compromising the bioavailability of a calcium intake, which is inadequate to meet the demands of the growing child. Healing of the biochemical and histological abnormalities in these children can be achieved by placing them on a normal diet with a calcium intake of approximately 1000 mg/day, without the addition of vitamin D supplements[20].

Several clinical and biochemical features differentiate privational rickets due to dietary calcium deficiency from that associated with vitamin D deficiency. Clinically, muscle weakness and hypotonia are characteristic features of vitamin D deficiency; these are absent in dietary calcium deficiency. Biochemically, vitamin D deficiency rickets is associated with low serum 25-OHD concentrations and generally low or normal 1,25-$(OH)_2$D levels[21], while in patients with dietary calcium deficiency serum 25-OHD levels are typically normal and 1,25-$(OH)_2$D values are elevated, which is the normal physiological response to inadequate intestinal calcium absorption and hypocalcaemia.

It is apparent from the above discussion that privational rickets is a spectrum of diseases ranging from pure vitamin D deficiency (as might occur in the unsupplemented breast-fed infant) at the one end of the spectrum to dietary calcium deficiency in the face of an adequate vitamin D intake at the other. In between these two extremes, lies the situation as it probably pertains to the Asian community in the UK and to a number of other at-risk communities. In these, low dietary calcium content or the poor availability of ingested calcium through the presence of phytate or other binding agents can precipitate vitamin D deficiency in situations where the vitamin D status is marginal.

The suggested pathogenesis of privational rickets in the Asian community might explain the apparent paradox of the reported finding of relatively normal serum concentrations of 1,25-$(OH)_2$D in the face of low 25-OHD levels[21]. Although a number of researchers consider other circulating vitamin D metabolites to have biological effects at physiological levels, it is generally believed that 1,25-$(OH)_2$D is by far the most active metabolite, which plays a central role in calcium homeostasis. Thus, in rickets due to vitamin D deficiency alone, 1,25-$(OH)_2$D levels would be

expected to be low, as the mechanism for the bone disease is considered to be the result of an inadequate intestinal absorption of dietary calcium, and the consequent hypocalcaemia and hypophosphataemia.

During the development of privational rickets due to a low dietary calcium intake or impaired intestinal calcium absorption (resulting from a high phytate or oxalate content) in the face of a sub-optimal vitamin D status, 1,25-$(OH)_2$D concentrations should initially be elevated as the individual attempts to maintain normal calcium homeostasis. These elevated 1,25-$(OH)_2$D levels increase the metabolic clearance rate of 25-OHD with a consequent increase in vitamin D requirements. As substrate (25-OHD) levels fall below that necessary to maintain the increased 1,25-$(OH)_2$D production, 1,25-$(OH)_2$D concentrations and intestinal calcium absorption decrease, which lead to the development of metabolic bone disease. At this stage serum 1,25-$(OH)_2$D levels might still be within the normal range but are inadequate to maintain an appropriate calcium absorption to meet the requirements of the growing skeleton. If the child presented with rickets at this time, serum 25-OHD levels would be within the vitamin D deficient range but 1,25-$(OH)_2$D values might be recorded as normal.

Thus privational rickets can no longer be considered to be the result of an inadequate vitamin D supply alone, but is the result of an imbalance of interrelated factors which are important in maintaining an optimal intestinal calcium absorption to meet the needs of the growing skeleton.

John M Pettifor
MRC Mineral Metabolism Research Unit,
Department of Paediatrics,
University of the Witwatersrand,
Johannesburg, South Africa

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Alcoholic brain damage

Specific neuropathological lesions such as central pontine myelinolysis, Marchiafava-Bignami syndrome and pellagra are well recognized causes of alcohol related brain damage. Here we shall concentrate on recent information implicating thiamine and the complex interactions between thiamine deficiency, ethanol neurotoxicity and genetic predisposition in the pathogenesis of chronic, often undiagnosed, brain damage.

Interactions between ethanol and thiamine are complex. Ethanol interferes directly and indirectly with the absorption, storage and utilization of thiamine, exacerbating thiamine deficiency. Thiamine deprivation in turn increases voluntary ethanol consumption in the rat, thus positive feedback occurs. It is thought that thiamine is used during the metabolism of ethanol (via the MEOS system induced in alcoholics) contributing to deficiency and that thiamine deficiency causes, via hypothalamic mechanisms, an increase in alcohol dehydrogenase activity and thus enhanced alcohol metabolism. The interplay between thiamine availability and alcohol metabolism is therefore underlined. Furthermore, there is evidence