Thoughts on the aetiology of vitamin D deficiency in Asians

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Following the virtual elimination of vitamin D deficiency in Britain earlier this century, rickets and osteomalacia began to be recognized with increasing frequency in the early sixties (Dunnigan *et al.*, 1962). The disease was almost entirely restricted to Asian subjects and was subsequently reported in all cities having a significant Asian population. The purpose of this review is to point out that most current theories not only fail to explain the occurrence of vitamin D deficiency in Asians, but also cannot adequately explain the deficiency occurring in liver and gastrointestinal disorders. A theory is put forward that more completely encompasses the known facts.

Facts about 'Asian' osteomalacia

- (1) Studies to date have always shown low serum 25-hydroxy-vitamin D (25-OH-D) concentrations (Preece *et al.*, 1973). The disease is therefore a true vitamin D deficiency state.
- (2) 25-OH-D concentrations fall when Asians come to Britain (Preece *et al.*, 1975) although normal levels are found in Asians in their homeland (Rashid *et al.*, 1983).
- (3) 25-OH-D concentrations rise during summer months in Asians and this may be associated with spontaneous resolution of the disease (Stamp and Round, 1974).
- (4) The most important dietary risk factors for the development of vitamin D deficiency is a high fibre, low meat diet (Dunnigan *et al.*, 1982).

Popular theories of vitamin D deficiency in Asians

Dietary deficiency of vitamin D

Asians have been reported to have lower vitamin D intakes in their diets (Hunt *et al.*, 1976). However, this has not been confirmed by other studies (Dunnigan and Smith, 1965). Studies have however shown that at least 90% of the 25-OH-D present in the blood originates from skin sources with dietary sources playing only a minor part (Haddad and Hahn, 1973, Preece *et al.*, 1975). For these reasons, a low dietary

intake of vitamin D alone would not be expected to cause appreciable changes in the vitamin D status of an individual.

Impaired skin production of vitamin D

West Indians in Britain do not suffer from clinical vitamin D deficiency. Skin pigmentation *per se* is therefore highly unlikely to be the cause of vitamin D deficiency. Although some Asians in Britain wear national costumes which cover much of the body, this is the exception in many cases, especially the children. Most Asian children seen with rickets wear Western style clothes (Heath, D.A., personal observations). Studies have often failed to show any obvious differences between daylight exposure between Asian and white children (Dunnigan, 1973) although more recent studies have shown that rachitic children have had less outdoor exposure than non-rachitic children (Dunnigan *et al.*, 1982). From this evidence it would be hard to incriminate a lack of sunlight exposure as the sole cause of vitamin D deficiency although it may be a partial factor. It certainly could not explain the occurrence of the disorder in Asia, Africa and the Middle East—countries where vitamin D deficiency occurs in the presence of plentiful sunlight. The fall in vitamin 25-OH-D concentrations in Asians coming to Britain is almost certainly due to the decreased amounts of ultraviolet light present in the more northern latitudes. Amounts of sunlight able to produce adequate supplies of vitamin D in white subjects are frequently inadequate in Asians. The importance of the skin for vitamin D production does indicate that subjects who have any other reason for developing vitamin D deficiency will become even more dependent on skin synthesis of vitamin D. Such people might develop a deficiency state with minor reductions in sunlight exposure.

Abnormal vitamin D metabolism

To date there is no evidence for this possibility.

High chapatti intake

Several studies have incriminated the development of vitamin D deficiency with high chapatti intake (Dunnigan *et al.*, 1982; Hunt *et al.*, 1976) and healing of rickets has followed the institution of a chapatti free diet (Ford *et al.*, 1972). Chapattis have a high phytate content, and most theories have linked a high phytate diet with a reduction in calcium absorption in the small intestine due to the complexing of calcium in the gut. Such a mechanism would not lead to vitamin D deficiency, and calcium deficiency *per se* does not cause rickets or osteomalacia in humans. Despite this, there is now overwhelming evidence linking vitamin D deficiency with the intake of a high phytate, high fibre diet. Dunnigan and his colleagues have reviewed the occurrence of vitamin D deficiency in various parts of the world both now and in the past and have put forward a convincing argument that the only common factor was the intake of a diet high in unextracted flour (Dunnigan *et al.*, 1982). They point out the occurrence of rickets and osteomalacia in Asia, Africa and the Middle East and the epidemics of the disease that occurred during and after the two World Wars in Europe; all associated with the use or change to a high extraction flour. Particularly persuasive was the occurrence of rickets and osteomalacia in Ireland in 1941 coinciding with the temporary increase in extraction rate of flour and hence a change from white to wholemeal flour (Jessop, 1950). More recently, vitamin D deficiency has been noted in people eating a lacto-vegetarian diet. In all these situations, there has been no evidence of sunlight deprivation.

Before trying to explain how such a situation produces vitamin D deficiency, it is perhaps pertinent to look at other, rarer, situations where vitamin D deficiency occurs. Other well-recognized situations are the elderly and in patients with gastro-intestinal and liver disease. Vitamin D deficiency in the elderly can readily be explained by a lack of exposure to sunlight and therefore is most commonly found in elderly institutionalized subjects. The explanation of vitamin D deficiency in gastro-intestinal disease such as coeliac disease, Crohn's disease and pancreatic disease has, in the past, been associated with either a failure to absorb vitamin D and/or calcium of dietary origin. As argued above, calcium deficiency *per se* would not give low blood vitamin D concentrations or osteomalacia, and a complete lack of dietary vitamin D would not cause a large fall in serum 25-OH-D provided skin synthesis was normal. In liver disease, osteomalacia has been most commonly associated with obstructive lesions especially primary biliary cirrhosis rather than the severity of hepatocellular function. For this reason, a failure of hepatic 25-hydroxylation is unlikely to be the explanation. It therefore appears that present theories fail to explain

the occurrence of vitamin D deficiency in the various gastro-intestinal and hepatic disorders.

A unifying explanation

Vitamin D, like many compounds in the body, undergoes an entero-hepatic circulation (Arnaud *et al.*, 1975). 25-OH-D formed in the liver is, in part, secreted into the bile and subsequently reabsorbed in the intestine. Such a situation has been well documented in animals and man although the magnitude of this process is unclear as yet in man. Following bolus intravenous injections of tracer amounts of radioactive vitamin D in humans, 12.4% of the radioactivity appeared in the bile during a 24-hr period (Ledger and Compston, 1983). Could an interference with the entero-hepatic circulation explain the development of vitamin D deficiency in Asians and in other situations?

An interference with the entero-hepatic circulation would reduce concentrations of 25-OH-D irrespective of the original source of vitamin D. Vitamin D sterols have chemical similarities to bile acids which are avidly bound by lignins and other materials found particularly in unextracted flour. Lignins are known to increase bile acid excretion (Eastwood and Hamilton, 1968)—might they also bind vitamin D sterols? *In vitro* studies show that uncooked flour, both white and brown, avidly binds labelled 25-OH-D (Sweeting and Heath, unpublished observations). Normal subjects studied on a normal or high fibre diet have a shorter half-life of injected tritiated 25-OH-vitamin D when on the high fibre diet (Batchelor and Compston, 1983). This is compatible with the idea that some of the vitamin is bound in the gut and eliminated. Cholestyramine, used to bind bile salts in the intestine, has been reported to cause vitamin D deficiency (Compston and Horton, 1978; Heaton and Barnard, 1972). The most logical explanation is that the drug, in addition to binding bile salts, also binds vitamin D compounds.

In the above examples, 25-OH-D secreted normally in the bile is complexed in the intestine and its absorption prevented.

In diseases of the small intestine, the break in the entero-hepatic circulation would be at the gut wall where the diseased bowel impedes absorption—a situation which causes a reduction in 25-OH-D blood concentrations irrespective of the dietary intake of vitamin D. It has been shown in a variety of malabsorptive conditions that the half-life of injected 25-OH-D is shortened and faecal losses increased (Batchelor, Watson and Compston, 1982; Compston *et al.*, 1982). Finally, in obstructive liver disease, there could be a barrier to the biliary excretion of 25-OH-

D into the intestine, or a failure of reabsorption due to the induced malabsorptive state.

Using such arguments, it now becomes possible to begin to put together a more logical explanation of the vitamin D deficiency states—high fibre diets, common to the Asian and Middle Eastern races, have the potential to bind vitamin D in the gut. Similar diets were also present in Europe at the end of the first and second World Wars, and in Ireland in 1944. The Asian therefore, under any circumstances, on such a diet loses excessive amounts of vitamin D in the stools and has greater requirements for the vitamin. On arrival in Britain, the reduced amount of sunlight reduces the skin production of vitamin D. This would account for the observations that 25-OH-D levels fall in Asians on arrival in this country, and that the vast majority of Asians have low blood vitamin D levels compared with white subjects exposed to similar amounts of sunlight but on a low fibre diet. Most do not develop clinical disease except when vitamin D requirements are greater, during rapid growth and pregnancy. The addition of modest supplements of dietary vitamin D is adequate to cover the interference in the entero-hepatic circulation.

The theory put forward appears to explain most, if not all, of the known facts concerning 'Asian osteomalacia'. It also more readily explains vitamin D deficiency occurring in malabsorptive and hepatic disorders.

Further studies will no doubt confirm or refute it. At the present time the ideas put forward so carefully by Dunnigan and his colleagues have much to commend them.

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