

PERSONAL VIEW

Are American Children Still Getting an Excess of Vitamin D?

Hyperreactive Children at Risk

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THE safety of vitamin-D supplementation has been the subject of editorials and statements by pediatric associations, both in Great Britain¹⁻⁷ and in the United States⁸⁻¹¹ for more than 12 years, ever since infantile hypercalcemia was correlated with hypervitaminosis D.** Fränk overdosed with vitamin D, and hyperreactivity to amounts of vitamin D far lower than those usually deemed toxic, have been implicated in the acute phase of infantile hypercalcemia, and also early in life by the normocalcemic disturbance characterized by supraaortic stenosis, involvement of other arteries, renal calcinosis and severe mental retardation, associated with an elfin facies. This combination of stigmata is often referred to as the Williams syndrome, or more frequently in the United States as the congenital supraaortic stenosis syndrome.**

Vitamin D-fortified milk has proven effective in eradicating rickets. The lower incidence of infantile hypercalcemia in America than in Great Britain may well be attributed to the addition of no more than 400 units of vitamin D per quart of milk since 1941,¹⁵ and to the repeated official*** recommendation that no more than 400 units of vitamin D, from all sources, be consumed daily.⁸⁻¹¹ This paper calls attention to evidence that the usual intake of vitamin D by American infants may not be universally safe, not only because of individual variation in response, but because of the addition of vitamin D to milk.

Early Studies on Daily Vitamin D Requirement and Effect of Vehicle

Several early findings on the safety and efficacy of vitamin D are startling in their implications. Vitamin D₂ (irradiated ergosterol or calciferol) was

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** For reviews, see references 10, 12-14.

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significantly more toxic in experimental animals than is natural (fish oil) vitamin D (vitamin D₃), particularly as regards cardiovascular and renal calcification.^{16, 17}

Even more significant are the data on the influence of milk on the dose of vitamin D required for prophylaxis and for cure of rickets. It was shown more than 30 years ago that the activity of vitamin D increased manifold when it was added to milk. Lewis¹⁸ observed, in 1935, that 90 units of crystalline vitamin D in milk were superior to those obtained with 900 units in oil in treating rachitic children. He commented that 10 to 15 drops of vitamin D in oil were necessary to cure rickets, whereas only one drop was necessary if it was incorporated in milk.

Stearns *et al.*¹⁹ reported, in 1936, that infants given 300 to 400 units of vitamin D in cod liver oil grew at faster than average rates, whereas infants getting all of their vitamin D from cod liver oil emulsified in milk grew at about the same rate on only 135 units per quart.

Drake²⁰ reported from Canada, the same year, that children of British and northern European stock were cured of moderate or advanced rickets by 300 units of vitamin D; they were fully protected by 95 units daily in irradiated milk, or 150 units as cod liver oil or viosterol.

Lewis²¹ found a considerable range in the amount of vitamin D necessary to prevent rickets in his population of New York City children of Negro, Puerto Rican and Italian derivation, the white children requiring less vitamin D than the black. Of 58 infants given 145 or 290 units in oil or in propylene glycol, 14 per cent and 10 per cent, respectively, developed moderate to severe rickets. When the same amounts of vitamin D were added to milk, only 5 per cent and 2 per cent exhibited early roentgenographic evidence of rickets. Among 42 infants who received 1,450 units of vitamin D in oil, only one (a Negro child) developed a mild form of the disease. To protect even such hyporeactive children from rickets, Lewis²¹ recommended that 332 units be added to

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milk to achieve the potency of at least 1,450 units in oil.

A later paper by Glaser *et al.*²² (1949) presented evidence that 100 units daily of all preparations of vitamin D in an oily vehicle were prophylactic against clinical rickets, even in premature and in Negro infants. However, because nine infants on that dose developed roentgenographic evidence or suspicion of rickets, among the 166 who were followed for eight months, the authors commented that 400 to 800 units (in oil) daily would allow a greater margin of safety in cases of illness or temporary neglect. The enhancing effect of milk, or of lactalbumin, on the potency of vitamin D was also shown in rats by Supplee *et al.*²³

A 1963 statement on vitamin D requirements by the Committee on Nutrition of the American Academy of Pediatrics pointed out that daily intakes of 250 units are at least as effective as larger intakes, and that 300 to 500 units daily are therapeutic.¹¹ The committee also recalled that prior to the era of supplementation and fortification of food with vitamin D, a balanced diet and outdoor play "practically always provided sufficient vitamin D to prevent detectible evidence of vitamin D deficiency . . ." (in the preschool and school child). In 1961 Bakwin⁹ observed that during spring and summer months when sunlight is ample and babies are exposed freely, no supplementation is necessary, and the use of vitamin D-reinforced milk is superfluous. That exposure to the sun of only the cheeks of fair-skinned infants and children, for as little as three hours daily, is probably sufficient to generate 400 units vitamin D, has recently been stated by Loomis.²⁴ On the other hand, Bakwin⁹ suggested that Negro infants might require vitamin D supplementation additional to that in fortified milk.

By 1953, irradiation of milk (which gave rise to vitamin D₂) was almost entirely superseded by addition of 400 units vitamin D₂ to each quart of fresh milk in most states.^{25, 26} Crystalline vitamin D₃ in equivalent amounts is added to evaporated milk by the major milk companies. Since the removal of the governmental restriction against such fortification of dried milk (recommended in 1966²⁷) an equivalent amount of vitamin D (usually D₃) is beginning to be added to many dried skim milks.

Potentialities of Risk of Vitamin D in Higher Than Prophylactic Doses

The amount of vitamin D that currently is added to almost all marketed fluid and dried milks delivers considerably more than prophylactic requirements for most infants; this dose even exceeds the amount needed to cure rickets in many cases.

Since the hazard of overuse of vitamin D was emphasized in 1961⁹ and in 1963,¹¹ the amount of vitamin D provided in vitamin concentrates and

added to other foods has been curtailed. Vitamin supplements, for example, now deliver up to 400 units daily. A recent analysis of consumption of vitamin D delivered by food and vitamin preparations²⁸ revealed that among infants, the daily vitamin D intake was from 130 to 914 units. In the preschool group, the range of intake was 21 to 1,137 units. In most instances, the major source of vitamin D was fortified milk.

A possibly significant corollary to the greater susceptibility of deeply pigmented infants to rickets is the seemingly greater frequency in fair-skinned children of infantile hypercalcemia, Williams syndrome, and possibly other sequelae such as renal calcinosis (see review¹⁴). For infants who are constitutionally hyperreactive, the amount of vitamin-D activity provided by 400 units added to a quart of milk may well be within the toxic range.

Reference should be made to Black's 1964 discussion¹² of theories to explain the metabolic abnormalities or variations that may be responsible for hyperreactivity to vitamin D. He also cautioned that the rat-bone line test (used for decades in the bioassay of vitamin D in milk) does not detect every agent in the serum which is capable of raising the serum calcium level of the infant. For example, although dihydroxycholesterol has the same activity in man weight for weight as has vitamin D, the rat-line test indicated only 1/400 of the activity of vitamin D.

More recent studies suggest that among the individual metabolic differences may be variations in ability to convert vitamin D or related cholesterol derivatives to active or to inert forms. Blunt *et al.*²⁹ have shown a metabolic product of vitamin D (25-hydroxycholecalciferol or 25-HCC) to be 40 per cent more active than its precursor. Possibly hyperreactive infants produce 25-HCC more effectively from vitamin D; hyporeactive infants may provide less, or may more effectively degrade vitamin D to inert metabolic products, as described by Avioli *et al.*³⁰

Taussig^{31, 32} has discussed the possibility that an inborn variation in man's ability to metabolize vitamin D may be responsible for the injury to the cardiovascular system seen, not only in infantile hypercalcemia and in supravalvular aortic stenosis, but also in other cardiovascular diseases.

Norman's³³ current view and evaluation of new laboratory work has led him to postulate that vitamin D does not act as a vitamin or as a cofactor for enzymes, but rather as a steroid hormone. Minimal alterations in its chemical structure may either increase or abolish its biologic activity.

A recent postulate to receive favorable consideration by a number of authorities^{8, 10, 13, 34} is that the initial metabolic and anatomic lesions of infantile hypercalcemia and supravalvular aortic stenosis syndromes are received *in utero*. These

proposals, initially made by clinicians who had recognized characteristics of infantile hypercalcemia in infants five to nine months old,^{35, 36} led to laboratory studies of the effect of excess vitamin D given to rabbits during pregnancy.³⁷ Pregnant animals who were given exceedingly high doses of vitamin D, and some of their offspring, developed aortic lesions resembling those seen in the human disease. Since the mothers of hypercalcemic infants, from whom histories of prenatal supplementation were available, had either received no vitamin D,³⁸ or vitamin D in amounts not over 1,000 units daily,^{13, 39, 40} this postulate is not proven.^{14, 41} However, whether or not hyperreactivity to vitamin D in the mother provokes the lesion in the fetus, exposure of hyperreactive infants to even moderately elevated vitamin D intake has been reported to cause lesions.^{13, 14, † 35, 38, 39}

In Great Britain, where hundreds of infants were reported to develop hypercalcemia during a period when they were given excessive amounts of vitamin D (calculated to be as high as 4,000 units daily in some instances),^{6, 7} halving the amount of vitamin D in dried milk formulas, and in other supplements, resulted in halving the incidence of hypercalcemia.¹ The disease, however, has not been eliminated.^{1, 2, 12, 14, 42, 43}

On the other hand, the incidence of rickets did not increase from the level reported before reducing the vitamin supplementation, during the same period of time, in an analysis that considered the colored immigrants separately.¹ The feeding histories of the immigrant children, however, revealed that they had not been fed the fortified infant foods to the same extent as had the native-born British children.^{1, 44}

Editorial approval was given to the compromise reached in providing vitamin supplementation at a level that protects against rickets in the majority of the population, and causes disease only in the minority of infants with lower than normal tolerance for this vitamin.²

The official position, in 1965, of the American Academy of Pediatrics, referring to their earlier acceptance¹¹ of the likelihood that vitamin D intake is related to infantile hypercalcemia and supravalvular aortic stenosis, was to recommend public health measures which may reduce the incidence of one form of mental retardation and one form of congenital heart disease.⁸ Such recommendations were considered justified only if a much larger normal population were not placed simultaneously in jeopardy from vitamin-D deficiency. Coleman,⁴³ who reported ECG changes in 12 of the 13 infants with hypercalcemia admitted to a Glasgow hospital in 1962-1963, has com-

† For details of cases of infantile hypercalcemia developing on daily intakes up to 2,000 units of vitamin D, see also references 43-45, 56, 61, 66, 67, 77, 91, 92, 95-98 in Seelig.¹⁴

mented that in selecting the prophylactic dose of vitamin D it is necessary to make responsible inquiry into the nature of the residual effects of vitamin D deficiency and toxicity, and to consider their relative importance. By the time infantile hypercalcemia is diagnosed, irreversible brain and cardiovascular damage may have developed. Rickets can be diagnosed early in the course of the disease; the early bone lesions can be reversed by appropriate therapy.

It is infinitely preferable to prevent both diseases, rather than to weigh the sociologic value of preventing one or the other. For the child whose brain and heart are permanently damaged, the frequency with which this happens is irrelevant. A concerted effort should be undertaken to develop simplified technics to ascertain the individual response to vitamin D very early in infancy. Supplementation with vitamin D, appropriate to individual requirements, should then be prescribed. The amount of vitamin D required for the prophylaxis of rickets in one child may be toxic for another.

There should be re-investigation of the delivered potency of the 400 units of vitamin D, added to milk. I have been able to find no disproof of the early work that showed markedly increased antirachitic activity of vitamin D in milk. We should exert every effort to develop an improved program which will prevent rickets without causing toxic reactions, even in a minority of our infant population.

References

1. Oppé, T. E.: Infantile hypercalcemia, nutritional rickets, and infantile scurvy in Great Britain; a British Paediatric Association report. *Brit. Med. J.* 1: 1659, 1964.
2. Editorial: Vitamin D as a public health problem. *Ibid.* 1: 1654, 1964.
3. Editorial: Aetiology of idiopathic hypercalcemia. *Ibid.* 1: 335, 1960.
4. Editorial: Idiopathic hypercalcaemia of infants. *Lancet* 2: 138, 1960.
5. Editorial: Infantile hypercalcaemia. *Brit. Med. J.* 1: 159, 1956.
6. Lightwood, R., Sheldon, W., Harris, C. and Stapleton, T.: Hypercalcaemia in infants; subcommittee report, British Paediatric Association report. *Lancet* 271: 136, 1956.
7. —, —, — and —: Hypercalcaemia in infants and vitamin D; subcommittee report, British Paediatric Association report. *Brit. Med. J.* 2: 149, 1956.
8. Committee on Nutrition, American Academy of Pediatrics: Vitamin D intake and the hypercalcemic syndrome. *Pediatrics* 35: 1022, 1965.
9. Bakwin, H.: The overuse of vitamins in children. *J. Pediat.* 59: 154, 1961.
10. Committee on Nutrition, American Academy of Pediatrics: The relation between infantile hypercalcemia and vitamin D; public health implications in North America. (Report written by Fraser, D.) *Pediatrics* 40: 1050, 1967.

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11. —: The prophylactic requirement and the toxicity of vitamin D. *Ibid.* 31: 512, 1963.
12. Black, J. A.: Idiopathic hypercalcaemia and vitamin D. *German Med. Monthly* 9: 290, 1964.
13. Fraser, D., Kidd, B. S. L., Kooh, S. W. and Paunier, L.: A new look at infantile hypercalcaemia. *Pediat. Clin. N. Amer.* 13: 503, 1966.
14. Seelig, M. S.: Vitamin D and cardiovascular, renal, and brain damage in infancy and childhood. *Ann. N. Y. Acad. Sci.* 147: 537, 1969.
15. Bing, F. C.: Vitamin D milk containing 600 USP units of vitamin D to the quart is not eligible for list of accepted foods. *JAMA* 116: 413, 1941.
16. Harris, R. S., Ross, B. D. and Bunker, J. W. M.: Histological study of hypervitaminosis D. *Amer. J. Dig. Dis.* 6: 81, 1939.
17. Morgan, A. F., Kimmel, L. and Hawkins, N. C.: A comparison of the hypervitaminoses induced by irradiated ergosterol and fish liver oil concentrates. *J. Biol. Chem.* 120: 85, 1937.
18. Lewis, J. M.: Clinical experience with crystalline vitamin D; the influence of the menstruum on the effectiveness of the antirachitic factor. *J. Pediat.* 6: 362, 1935.
19. Stearns, G., Jeans, P. C. and Vandecar, V.: The effect of vitamin D on linear growth in infancy. *Ibid.* 9: 1, 1936.
20. Drake, T. G. H.: Comparison of the antirachitic effects on human beings of vitamin D from different sources. *Amer. J. Dis. Child.* 53: 754, 1937.
21. Lewis, J. M.: Further observations on the comparative antirachitic value of crystalline vitamin D administered in milk, corn oil, or in propylene glycol. *J. Pediat.* 8: 308, 1936.
22. Glaser, K., Parmelee, A. H. and Hoffman, W. S.: Comparative efficacy of vitamin D preparations in prophylactic treatment of premature infants. *Amer. J. Dis. Child.* 77: 1, 1949.
23. Supplee, G. C., Ansbacher, S., Bender, R. C. and Flanigan, G. E.: The influence of milk constituents on the effectiveness of vitamin D. *J. Biol. Chem.* 114: 97, 1936.
24. Loomis, W. F.: Skin-pigment regulation of vitamin D biosynthesis in man. *Science* 157: 501, 1967.
25. Wickel, K. G.: Theory and practice of vitamin D fortification of milk. *Quart. Rev. Pediat.* 8: 224, 1953.
26. Spur, B.: Laboratory evaluation and control of homogenized and vitamin D milk. *Ibid.* p. 240.
27. Council on Foods and Nutrition: Fortification of nonfat milk solids with vitamins A and D. *JAMA* 197: 1107, 1966.
28. Dale, A. E. and Lowenberg, M. E.: Consumption of vitamin D in fortified and natural foods and in vitamin preparations. *J. Pediat.* 70: 952, 1967.
29. Blunt, J. W., De Luca, H. F. and Schnoes, H. K.: 25-hydroxycholecalciferol; a biologically active metabolite of vitamin D. *Biochem.* 7: 3317, 1968.
30. Avioli, L. V., Williams, T. F., Lund, J. and De Luca, H. F.: Metabolism of vitamin D₃-³H in vitamin D-resistant rickets and familial hypophosphatemia. *J. Clin. Invest.* 46: 1907, 1967.
31. Taussig, H. B.: Possible injury to the cardiovascular system from vitamin D. *Ann. Intern. Med.* 65: 1195, 1966.
32. —: On the evolution of our knowledge of congenital malformations of the heart. *Circulation* 31: 768, 1965.
33. Norman, A. W.: The mode of action of vitamin D. *Biol. Rev.* 43: 97, 1968.
34. Rowe, R. D. and Cooke, R. E.: Vitamin D and craniofacial and dental anomalies of supra-valvular stenosis. *Pediatrics* 43: 1, 1969.
35. Garcia, R. E., Friedman, W. F., Kaback, M. M. and Rowe, R. D.: Idiopathic hypercalcaemia and supra-valvular aortic stenosis. *New Eng. J. Med.* 271: 117, 1964.
36. Jue, K. L., Noren, G. R. and Anderson, R. C.: The syndrome of idiopathic hypercalcaemia of infancy with associated congenital heart disease. *J. Pediat.* 67: 1130, 1965.
37. Friedman, W. F. and Roberts, W. C.: Vitamin D and the supra-valvular aortic stenosis syndrome; the transplacental effects of vitamin D on the aorta of the rabbit. *Circulation* 34: 77, 1966.
38. Stapleton, T., Macdonald, W. B. and Lightwood, R.: Management of "idiopathic" hypercalcaemia in infancy. *Lancet* 1: 932, 1956.
39. Schlessinger, B. E., Butler, N. R. and Black, J. A.: Severe type of infantile hypercalcaemia. *Brit. Med. J.* 1: 127, 1956.
40. Wiltse, H. E., Goldbloom, R. B., Antia, A. U., Ottesen, O. E., Rowe, R. D. and Cooke, R. E.: Infantile hypercalcaemia syndrome in twins. *New Eng. J. Med.* 275: 1157, 1966.
41. Editorial: Supra-valvular aortic stenosis. *JAMA* 198: 1302, 1966.
42. Barr, D. G. D. and Forfar, J. O.: Oral calcium-loading test in infancy, with particular reference to idiopathic hypercalcaemia. *Brit. Med. J.* 1: 477, 1969.
43. Coleman, E. N.: Infantile hypercalcaemia and cardiovascular lesions; evidence, hypothesis, and speculation. *Arch. Dis. Child.* 40: 535, 1965.
44. Bransby, E. R., Berry, W. T. C. and Taylor, D. M.: Study of the vitamin-D intakes of infants in 1960. *Brit. Med. J.* 1: 1661, 1964.