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Vegetarianism and vitamin B-12 (cobalamin) deficiency¹⁻⁴

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Vegetarian diets can be classified as either lactovegetarian, ovovegetarian, lactoovovegetarian, or vegan if they include, respectively, dairy products, eggs, both dairy products and eggs, or no animal products at all. Vegan diets have a very low cobalamin content, but a study by Herrmann et al (1) in this issue of the Journal forces us to reevaluate the shortcomings of the other forms of vegetarianism. Herrmann et al show that vegans and, to a lesser degree, lactoovovegetarians and lactovegetarians have biochemical evidence of cobalamin deficiency based on increased blood total homocysteine and methylmalonic acid (2-4) and low holotranscobalamin II concentrations; the test for the latter is still under investigation for addition to the diagnostic algorithm for vitamin B-12 deficiency (5). The adverse health consequences in 2 closely related groups, voluntary vegetarians who base their dietary preferences on religious or philosophical grounds and persons whose near-vegetarianism is imposed by poverty, are worth reexploring. Worldwide, vegetarians number in the hundreds of millions, so public health initiatives that seek to improve the health of this population will have a global effect.

Whereas vegetarianism is present in all geographic areas, only in the past 50 y was it recognized that vegetarians have consistently lower vitamin B-12 concentrations than do nonvegetarians and that vegetarians are at greater risk of vitamin B-12 deficiency than are nonvegetarians. Because vitamin B-12 is produced in nature only by vitamin B-12-producing microorganisms, humans must receive vitamin B-12 solely from the diet (3). Although there are abundant vitamin B-12-producing bacteria that colonize the large bowel, that organ is too distal to allow normal vitamin B-12 absorption. Herbivores obtain vitamin B-12 primarily from plants contaminated with nitrogen-fixing, vitamin B-12-producing bacteria that grow in roots and nodes of legumes and from plants contaminated with feces. Carnivorous lower animals receive their vitamin B-12 by eating insects and other animals and via coprophagy. Nonvegetarians obtain most of their vitamin B-12 through eating meat, whereas lactoovovegetarians obtain most of their vitamin B-12 from milk, dairy products, and eggs. Plants contaminated with vitamin B-12-producing bacteria through fertilization with manure may also be a source of vitamin B-12, so, in theory, "organically grown" leafy vegetables may have higher vitamin B-12 concentrations than do leafy vegetables exposed to chemical fertilizers.

Nonvegetarians in the developing world also obtain only marginal amounts of vitamin B-12 (6), because meat is expensive and those in the middle- and lower-income brackets cannot afford this luxury with any regularity. Moreover, a steak that is considered an average size for consumption by one person in the United States commonly feeds 6-8 persons when made into a stew or curry in the developing world. So professed nonvegetarians in developing countries often have a vitamin B-12 status that is only

marginally better than that of lactoovovegetarians, and only daily meat eaters have vitamin B-12 status similar to that of nonvegetarians in the West (7).

In 1955, Wokes et al (6) systematically compared a group of US, Dutch, and British vegans with nonvegetarians from those same countries and found that many of the vegans had significantly lower vitamin B-12 concentrations than did the nonvegetarians. A year later, Dhopeswarkar et al (8) observed that asymptomatic Indian lactovegetarians, who make up more than half of the Indian population, had distinctly lower serum vitamin B-12 concentrations than did nonvegetarians. This was confirmed by studies from different geographic regions in India (7, 9-11). Those who only occasionally ate meat had vitamin B-12 concentrations intermediate to those of lactoovovegetarians and nonvegetarians who frequently ate meat (7). Thus, the use of nonvegetarian cohorts in which most persons are "occasional meat eaters" could potentially account for the equally poor vitamin B-12 status of nonvegetarians and vegetarians in studies reported from the developing world (12, 13). Because vegetarianism has been widely practiced for several millennia in India, much of the population of that country is at risk of having low vitamin B-12 status throughout life. The superimposition of other conditions that perturb either vitamin B-12 absorption, eg, partial gastrectomy or bypass, proton-pump inhibitors, and ileal disease or surgical resection, or vitamin-B12 metabolism, eg, nitrous oxide exposure, can easily tip such persons into frank vitamin B-12 deficiency much earlier than in nonvegetarians who have replete cobalamin stores (3).

Although earlier reports consistently identified a lower vitamin B-12 concentration in lactovegetarians than in nonvegetarians, in the absence of clinical findings, it was difficult to confidently characterize that characteristic as representing a vitamin B-12-deficient state. That difficulty changed with the availability of plasma metabolite tests, but the ultimate proof that a deficiency existed must be the complete normalization of subsequent test results after the replacement of specific vitamins (4). Nevertheless, on the basis of what we know of the vitamin B-12 content of vegetarian diets, it seems likely (and Herrmann et al posit) that

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² Dedicated to the memory of Victor Herbert (1927-2002), whose sustained investigations of clinically relevant issues related to vitamin B-12, folate, and one-carbon metabolism earned him respect, admiration, and status as one of the giants in this field. (Internet: <http://www.victorherbert.com>, accessed 4 March 2003.)

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asymptomatic subjects who were found to be “normal” in earlier studies using vitamin B-12 concentrations as an indicator of cobalamin status would have been found to be vitamin B-12 deficient had more sophisticated metabolite tests been used.

Pathologic associations between nutritional vitamin B-12 deficiency and disease were sporadically reported from the West (14). Yet in 1975 the general assumption was that lactoovovegetarians in the West generally had no special problems in obtaining adequate vitamin B-12 in their diet (15). Nevertheless, the 1985 report on 138 Hindu vegetarians living in the United Kingdom with clinical evidence of vitamin B-12 deficiency (16) continued to highlight the low cobalamin status of vegetarian diets.

What has been termed a subclinical state of vitamin B-12 deficiency should be revisited in the light of the availability of far more sophisticated questionnaires, instruments, and other methods used to test brain function. Investigators have consistently found abnormalities in electroencephalography, evoked potentials, and P300 event-related potentials (electric signals from the brain that are found during the performance of various cognitive tasks and measured as an electrophysiologic marker of cognitive ability) in one-half or more of those with metabolically defined mild preclinical cobalamin deficiency (17–19). In most cases these abnormalities were reversed with cobalamin therapy, which supported the hypothesis of a causal relation.

The existence of clear-cut biochemical evidence of perturbed vitamin B-12 metabolism in vegetarians and the fact that hyperhomocysteinemia is a risk factor for occlusive vascular diseases (20), some neural tube defects (21), congenital heart defects (22), and dementia and Alzheimer disease (23) should spur even the most skeptical vegetarian to efforts to reverse an easily preventable dietary deficiency of vitamin B-12. Yet, studies on unique groups in the West such as Seventh-Day Adventists that showed the extent of poor cobalamin status (24) also highlighted the difficulty of persuading even highly educated populations that are at risk to routinely take cobalamin supplements (25, 26).

Given the likelihood that low vitamin B-12 status is widespread, it is not surprising that infants born to vitamin B-12-deficient vegetarian mothers would also be at risk of cobalamin deficiency. This is particularly relevant in the developing world, where prolonged breastfeeding over the first 2 y is common practice. A syndrome of nutritional dystrophy and anemia, first described in 1957, was found exclusively among breastfed infants of Indian mothers of extremely low socioeconomic status (27). Although these infants had adequate general nutrition, they also had apathy, megaloblastic anemia, skin hyperpigmentation, involuntary movements, and developmental regression that were rapidly corrected by vitamin B-12. Many of these features would be characteristic of the findings among breastfed, vitamin B-12-deficient infants of mothers in the West who consumed a macrobiotic diet. A 1962 study in South India of 6 breastfed infants who had a similar syndrome and whose mothers were asymptomatic vegetarians found that vitamin B-12 concentrations were low in both the serum and the breast milk of the mothers (28). This vitamin B-12-responsive syndrome has been extensively reported throughout India (29), and similar cases have been described in the West (30). The latter report documented low vitamin B-12 concentrations and biochemical evidence of increased metabolites in both mother and infant, which highlighted “the importance of educating strict vegetarians about the deficiency of vitamin B12 in their diets and the importance of vitamin B12 supplementation” (30). Evidence has accumulated that the fetus is dependent on the mother for cobalamin

(31, 32), and the longer the mother has been a vegetarian, the greater the likelihood that she will have low maternal serum and greater milk cobalamin concentrations that closely correlate with cobalamin insufficiency in the infant (33–35).

A longitudinal cohort study reported the development of vitamin B-12 deficiency in infants who consumed a macrobiotic diet (36). The same investigators showed that 15-mo-old infants in a cohort consuming a macrobiotic diet had markedly impaired cobalamin status and impaired psychomotor functioning (37). Whereas most of the families switched their children to a lacto-vegetarian, lactoovo-vegetarian, or even omnivorous diet and did so, on average, after the infant’s sixth birthday, one-fifth of these children continued to have impaired cobalamin status (38). Later, this group showed that cognitive functioning continued to be affected in adolescents aged 10–16 y who had been switched to a lacto-vegetarian or omnivorous diet by their sixth birthday (39). The most important associations were between cobalamin status and performance on tests of fluid intelligence, which involves the use of faculties related to reasoning, abstract thinking, and learning ability (39). Thus, compromised vitamin B-12 status during childhood (< 6 y of age) has potential negative consequences well into adulthood.

Reports on nutritional macrocytic anemia identified vitamin B-12 deficiency as the basis for anemia in $\leq 50\%$ of Indian children aged 6 mo to 12 y who were studied (40), and one-fifth of anemic children aged 3 mo to 3 y in an urban Indian slum had vitamin B-12 deficiency as shown by serum concentrations (41). It is likely that metabolite testing would have identified many more asymptomatic vitamin B-12-deficient children, because only anemic children were studied, and there is probably widespread low vitamin B-12 status among children in India. Parallel results came from a study of Guatemalan schoolchildren (42). In an earlier study in Guatemala, vitamin B-12 deficiency was highly prevalent in lactating women and was associated with deficiency of the vitamin in their infants (43). Guatemalan children continue to have low vitamin B-12 status through either dietary insufficiency alone or a combination of that status and as yet uncharacterized gastrointestinal malabsorption (42). The risk of poor cognitive and neuromotor performance is real among these children with low vitamin B-12 status (44), in whom reasoning, short-term memory, and perception were worse than they were in the group with adequate vitamin B-12 (45). This study is instructive because Guatemalan children can be seen as representatives of the status of poverty-imposed near-vegetarianism that is prevalent throughout the developing world. Collectively, the adverse consequences of vitamin B-12 deficiency in children fed vegetarian diets and in those with poverty-imposed near-vegetarianism have significant implications for millions of children worldwide.

Recent studies that have begun to revisit issues related to the bioavailability of vitamin B-12 in dairy products and fortified grain are encouraging (46). Whereas intake from vitamin B-12 supplements and fortified cereals appears to be protective against low vitamin B-12 status (47), we still lack prospective trials to define the optimum diet for various at-risk populations. Nagging questions persist. How can the conversion of vitamin B-12 to inactive analogues as a result of multivitamin-mineral chemical interactions (48, 49) or interaction with foods and other nutrients be avoided? Does the cooking of certain “ethnic-specific” foods containing vitamin B-12 lead to conversion to vitamin B-12 analogues? What is the influence of large-scale processing on the



shelf life and subsequent bioavailability of foods fortified with vitamin B-12?

Clearly, recommendations for supplementation of vitamin B-12 are not that easily implemented, as witnessed by the continued documentation of probable vitamin B-12 deficiency among vegetarians described in this issue of the Journal. Nevertheless, the data are compelling, and they indicate that vegetarians should routinely take cobalamin or vitamin B-12 supplements, which in their generic form are relatively inexpensive. In developing countries, other formidable problems were incurred in attempts to implement a program of supplementation of other vitamins (50). Yet the lack of a comprehensive initiative to protect vegetarians from vitamin B-12 deficiency can lead to a whole generation of cobalamin-deficient children (and adults) who are incapable of making good decisions because of the additional burden of neurologic deficits induced by cobalamin deficiency. The international nutrition community must take up the challenge posed by this body of evidence and enact practical steps to ensure parity in the vitamin B-12 status of vegetarians and omnivores. 

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