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VITAMIN B12 DEFICIENCY AS A WORLDWIDE PROBLEM

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■ **Abstract** Pernicious anemia is a common cause of megaloblastic anemia throughout the world and especially in persons of European or African descent. Dietary deficiency of vitamin B12 due to vegetarianism is increasing and causes hyperhomocysteinemia. The breast-fed infant of a vitamin B12–deficient mother is at risk for severe developmental abnormalities, growth failure, and anemia. Elevated methylmalonic acid and/or total homocysteine are sensitive indicators of vitamin B12–deficient diets and correlate with clinical abnormalities. Dietary vitamin B12 deficiency is a severe problem in the Indian subcontinent, Mexico, Central and South America, and selected areas in Africa. Dietary vitamin B12 deficiency is not prevalent in Asia, except in vegetarians. Areas for research include intermittent vitamin B12 supplement dosing and better measurements of the bioavailability of B12 in fermented vegetarian foods and algae.

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INTRODUCTION

Vitamin B12 nutrition has two unique features that pose problems for human nutrition: One is the unique human autoimmune disease pernicious anemia (PA), and the other is the virtual restriction of B12 to foods of animal origin. Vitamin B12 (cobalamin) is one of a group of complex molecules with a cobalt-containing corrin ring synthesized only by microorganisms (136). Current methods of B12 analysis measure, to some extent, inactive corrinoids in addition to vitamin B12. Plants do not use or contain vitamin B12. When the two B12-dependent enzymes lack their B12 cofactors, two metabolites, homocysteine and methylmalonic acid, increase (154). The usual dietary source of vitamin B12 for omnivores is flesh of other animals. Feces contain large amounts of corrinoids, including some true vitamin B12 (72, 136). Ruminants are unique in that microorganisms in the rumen synthesize vitamin B12 as long as they have a cobalt source.

Vitamin B12 is bound to enzymes in food and must be released by the action of gastric enzymes and acid prior to being bound by intrinsic factor, a protein synthesized by gastric parietal cells, which is taken up in the distal ileum (9). PA is due to the autoimmune loss of secretion of intrinsic factor, which causes a severe, previously fatal, vitamin B12 deficiency. The pathophysiology of vitamin B12 deficiency in humans has been studied in patients with PA who generally have otherwise normal nutritional status. They develop a macrocytic anemia with characteristic abnormalities in all of the cell lines in the bone marrow. Because the megaloblastic anemia resembles that caused by folate deficiency and responds to pharmacologic doses of folic acid, it can be difficult to recognize B12-deficient megaloblastic anemia (9). In addition, approximately 30% of patients with PA have signs and symptoms of spinal cord, cranial or peripheral nerve, or cerebral demyelination. The severity of megaloblastic anemia and the central nervous system disease is inversely correlated, which prevents recognition of vitamin B12 deficiency if megaloblastic anemia is used as the indicator of deficient status (71, 153). Vitamin B12–deficient infants and younger children may also show movement disorders. Symptoms in infants include irritability, abnormal reflexes, feeding difficulties, obtundation progressing to coma, and, because of the failure of brain

growth, permanent developmental disabilities if diagnosis is delayed (65, 118, 123). It is important to recognize and treat PA because adequate vitamin B12 replacement will cure megaloblastic anemia and improve the central nervous system disease. The recognition and treatment of milder forms of vitamin B12 deficiency may also be important because hyperhomocysteinemia is a risk factor for vascular disease and cognitive impairment.

Studies of methylmalonic acid and total homocysteine values as compared to vitamin B12 levels in patients with PA have proven that the metabolites are elevated prior to development of any clinical abnormalities and often prior to abnormal serum vitamin B12 (106). In general, however, the lower the serum vitamin B12 level the more likely it is that a deficiency exists. Emphasis in this review is placed on the more recent literature measuring both metabolite and vitamin levels. The contribution of vitamin B12 deficiency to nutritional anemia worldwide has probably been underestimated because of the frequent coexisting deficiencies of iron, folate, and other vitamins resulting from diets low in animal protein. Iron deficiency and thalassemia both mask macrocytosis, even when vitamin B12 deficiency is severe (9). In addition, nutritional anemia rarely responds to the replacement of only one of multiple missing nutrients (7).

The above discussion illustrates many of the issues involved in a review of worldwide vitamin B12 status. PA, other malabsorption syndromes, and varying dietary intakes all play a role in the prevalence of vitamin B12 deficiency. Vitamin B12 deficiency is a continuum of asymptomatic metabolic abnormalities ranging to life-threatening clinical syndromes, and thus many diagnostic parameters can be used to describe deficiency.

VITAMIN B12 DEFICIENCY CAUSED BY MALABSORPTION: GEOGRAPHIC DISTRIBUTION OF PERNICIOUS ANEMIA

It is often stated that PA is most common in Northern Europeans, with special emphasis on a high prevalence in Scandinavian countries in which the most detailed epidemiological studies have been performed (37, 38). However, over the past 20 years, studies have shown a high prevalence in people of African descent. Also, many reports from around the world show that PA is the major cause of megaloblastic anemia (38, 153). If diagnosis of PA is based on the most rigorous definition, i.e., megaloblastic anemia and malabsorption of vitamin B12 corrected with intrinsic factor in the Schilling test, then the true prevalence will be underestimated because patients may have neurologic rather than hematologic disease, and Schilling tests are either unavailable or have methodologic difficulties (56). Serum antibodies to intrinsic factor are highly specific but only 50% sensitive (9). PA incidence increases with age, but certain races or ethnic groups may present at younger ages (see United States, Africa, and Middle East sections below) (38).

TABLE 1 Reported frequency of pernicious anemia per 100,000

Country	Prevalence	Incidence*	Reference
United Kingdom	50–200		37
Denmark	130	9.5	133
Sweden	198		24
United States	151		87
Minnesota		49.2 F 25.1 M	61
Boston seniors	2900		98
California seniors	4000 white F 4300 black F 2300 white M 1800 black M 0/99 Asian		30
Southwestern Indians			159
>60 y	340		
Hawaii (Japanese)		1.0	60
Hong Kong		5.5	42
Curaçao		19	173

*Per year.

F, female; M, male.

Northern Europe

The frequency of PA in the United Kingdom (37) was reported to range from 50–200 per 100,000 (see Table 1). A report from Odense County in Denmark showed a prevalence of 0.13%, with a female predominance. The incidence was shown to be 9.5 per 100,000 inhabitants per year (133). The prevalence of PA was 0.198%, with a marked age peak between ages 70 and 80 in Sweden (24).

United States

Researchers have studied the relative frequencies of PA in different racial and ethnic groups in the United States. The prevalence of PA cases among total hospital admissions was highest for immigrants from Scandinavia, England, and Ireland, and less frequent among those from Italy, Germany, France, and Portugal (59). The prevalence of PA in the United States was estimated at 151 per 100,000 (87). The incidence of PA was 49.2 per 100,000 (women) and 25.1 per 100,000 (men) per year in Rochester, Minnesota (61). Seniors of unspecified race and ethnicity in Boston had a prevalence of 2.9% of positive intrinsic factor antibodies (98). Interesting racial information about PA patients was reported from Los Angeles, where 47% were European, 33% were African American, and 31% were Latin American (33). The authors noted that the Europeans were mainly British or Scandinavian, but also present in the cohort were Irish, Italian, Jewish, German, Polish, Dutch, Austrian,

Russian, Basque, and individual Syrian and Lebanese subjects. The age was lower in African American and Latin American female PA patients as compared to the Europeans (33). A similar racial profile was seen in 310 New York hospital patients with PA, 41% of whom were African American, 33% white, and 25% Latino, percentages that reflected the catchment area (154). A review of patients with B12-deficient neurologic disease showed that 43% were African American, 39% white, and 16% Latino, of whom most were Caribbean Hispanics from Puerto Rico or the Dominican Republic (71). A California study of seniors showed that previously undiagnosed PA was 4% in white women, 4.3% in African American women, 2.3% in white men, and 1.8% in African American men (30). No cases were found in the 99 subjects who were predominantly Asian American. There were also no cases in the Hispanics who were primarily from Mexico or Central America. PA in Southwestern Native Americans was reported to have a minimum prevalence of 0.19% in those over age 50 and 0.34% over age 60 (159).

Africa

Over the past three decades there has been an increasing awareness and diagnosis of PA in African populations. In 1973, researchers in South Africa described patients who had megaloblastic anemia with anti-intrinsic factor antibodies, but because of coexisting malabsorption syndromes, the authors were hesitant to describe them as true PA cases (76, 77). A series comparing PA in black patients from Washington, D.C., and Johannesburg, South Africa, drew attention to the young age of the African women at presentation who also had a high prevalence of anti-intrinsic factor antibodies and severe neurologic symptoms (160). Severe B12-deficient megaloblastic anemia was probably due to PA in 80% of patients from Gambia (1). Another report from Nigeria in 1992 described 11 patients with PA and remarked that most had been seen during the past three years, which the authors attributed to better recognition of PA (3). PA was the most common cause of megaloblastic anemia in hospitals in Harare, Zimbabwe (153). Severe B12 deficiency was confirmed by elevated methylmalonic acid and total homocysteine values, and the severity of the anemia was inversely related to the severity of the neurologic impairments (153). The extreme severity of megaloblastic anemia and neurologic problems described from Africa suggests that these cases are only the tip of the iceberg.

Middle East

PA was the cause of megaloblastic anemia in 69% of 203 patients admitted to six Israeli hospitals over 15 years (178). A 1970 report from Kuwait described four cases of PA, and the authors suggested that it was underdiagnosed in Arabs (5). PA caused megaloblastic anemia in 18 of 25 cases reported from Saudi Arabia; mean age was low (51 years), and the frequency of anti-intrinsic factor antibodies was very high, 89% (70). Another report from the United Arab Emirates described six PA patients with a mean age of 47 that were discovered over a three-year period. Five of the subjects had signs or symptoms of neurologic dysfunction and abnormal

nerve conduction (124). Among 200 patients admitted for anemia in a hospital in Turkey, 44 were found to have megaloblastic anemia caused by probable PA (95).

India

Megaloblastic anemia has long been attributed to nutritional folate deficiency in India (18). However, Asian Indian immigrants to Great Britain are often diagnosed with PA. One report found 2 of 15 cases of megaloblastic anemia had PA (25), 3 of 25 had PA in another report (26), and 20 of 138 had PA in the largest series (39). The reports from Great Britain prompted reports of cases of PA in India. A Bombay series describes 16 patients (7 with neurologic abnormality), average age 49 years, who were seen over an eight-year period (50).

Asia

A report from Singapore described six cases (four Chinese, two Asian Indian) of rigorously proven PA of 40 consecutive cases of megaloblastic anemia seen over three and a half years (88). A report from Hong Kong suggested that PA was rare because only three cases had been found between 1949 and 1965. However, the authors also found that 5% of 102 patients with thyrotoxicosis had anti-intrinsic factor antibodies; thus, PA may have been previously unrecognized in China (85). In a series from Taiwan, researchers studied urinary methylmalonic acid in 10 patients with severe B12-deficient megaloblastic anemia, which was likely PA (79). PA caused the megaloblastic anemia in 58 of 84 consecutive patients in Hong Kong (16). The patients had associated autoimmune features similar to those reported in white populations. At least 44 subjects with confirmed PA were reported in one year from the Prince of Wales Hospital in Hong Kong, which served a population of 800,000. Thus the incidence could be 5.5 per 100,000 per year, which is likely an underestimate because most of those with low B12 levels were not tested further (42).

In a report from Hawaii, researchers described five well-documented cases of PA over a nine-month period (with an average of 5300 patients admitted per year), which suggests that PA might be underdiagnosed in Japanese patients. The incidence could be as high as 1 per 1000 in Japanese Hawaiians (60). Four patients with PA and four with postgastrectomy B12 deficiency were reported in a study from Japan (96).

No cases of vitamin B12 deficiency or PA were found in 1562 Fijian subjects and one case of PA was reported in 1536 Asian Indians living in Fiji (27).

The sparse data available from Asia and Asian Americans suggest that the prevalence of PA is lower in Asians compared to the other races.

Mexico and Central and South America

Only one report of PA came from the region of Mexico and Central and South America. The report was from Curaçao in 1969, and it described 38 PA patients of

African descent from a population of about 100,000 persons over two years, thus about 19 per 100,000 per year, which would be even higher than the prevalence in Scandinavia (173). The data from Los Angeles and New York that showed 30% of PA patients were Latinos suggest that the lack of reports probably is not indicative of an absence of PA in these countries (33, 154).

Vitamin B12 Malabsorption Caused by Tropical Sprue

Tropical sprue is endemic in South India, epidemics occur in the Philippines, and it is prevalent in the Caribbean (57). American visitors to endemic areas may develop tropical sprue with vitamin B12 malabsorption that corrects after returning to the United States (107, 108). Tropical sprue caused vitamin B12 deficiency in 39 of 406 patients in the large series from New York (154).

Vitamin B12 Malabsorption Caused by Parasitic Infection

The fish tapeworm *Diphyllobothrium latum* is a rare cause of vitamin B12–deficient megaloblastic anemia because the worm is able to take up vitamin B12 from the small intestine. Generally, heavy infestations for long periods are required to deplete the host of vitamin B12. The infections have been described mostly in Northern Europe, Finland, Russia, Scandinavia, the Great Lakes region in the United States, and Japan. The recent popularity of raw fish ingestion has led to a resurgence of these infestations (121, 156).

Giardia lamblia, which causes chronic diarrhea and malabsorption syndromes, is a common protozoal intestinal infection throughout the world. Approximately one third of a group of children with chronic giardiasis had decreased absorption of vitamin B12, although plasma B12 was normal in a study from Denmark (132). Plasma vitamin B12 levels were high normal in a group of Spanish children with *Giardia* infestation, but increased further after vitamin B12 treatment. Thus malabsorption because of *Giardia* in well-nourished healthy populations is not a major cause of B12 deficiency (130).

Protein-Bound Vitamin B12 Malabsorption and the Elderly

There is a high prevalence (up to 15%) of elevated methylmalonic acid and associated low or low normal vitamin B12 values in elderly populations in the United States and Europe (69, 80, 89, 90, 109, 134, 140, 176). Most of such subjects do not have anti-intrinsic factor antibodies and probably do not have true PA. These patients may have atrophic gastritis and malabsorption of food-bound vitamin B12, although many questions remain unanswered (reviewed in Reference 31). Dietary intake of vitamin B12 is not decreased in the elderly in developed countries (10, 69, 80). However, low animal food intake was found to be a risk factor for predicting elevated methylmalonic acid in frail seniors receiving nutrition services in the United States (89). Synthetic vitamin B12 intake >12–30 ug/day decreased the risk for elevated methylmalonic acid or low vitamin B12 values in seniors (140,

163). Large doses of oral vitamin B12 are necessary to normalize methylmalonic acid values in most B12-deficient seniors (139), which supports the concept that malabsorption causes vitamin B12 deficiency in this group. Serum vitamin B12 is higher and methylmalonic acid is lower in elderly African Americans compared with whites (163). Elderly Asian Pacific Islanders had higher vitamin B12 levels than did African Americans or whites in other screening studies (32, 140). Latinos in the United States have a high prevalence of low plasma vitamin B12 associated with elevated serum gastrin, which suggests that atrophic gastritis is a problem in that ethnic group also (28, 32).

Less information is available about B12 deficiency in elderly persons in underdeveloped areas of the world. Indigenous Guatemalan seniors had a mean vitamin B12 of 254 pmol/L with 38% <150 pmol/L (93), which is considerably lower than the mean concentrations in U.S. Latinos (28). The mean serum vitamin B12 was also low in elderly men (168 pmol/L) and women (240 pmol/L) from Chile, with 51% of the men and 31% of the women <148 pmol/L. Despite having lower values, the men reported a mean daily B12 intake of 4.4 (131). After food folate fortification in Chile, the homocysteine correlated inversely with vitamin B12 and less so with folic acid in seniors, which raised concerns about possible masking of B12 deficiency (78). Cerebrovascular and neurologic disease and cognitive impairment were more common in Israeli elders in the lowest vitamin B12 category, <250 pmol/L (158).

A definite or possible B12 deficiency was found in 75% of elderly vegetarians in Hong Kong, with anemia in 48% of those with serum methylmalonic acid >1000 nmol/L (101). The mean plasma B12 in elderly Chinese in Singapore was 292 pmol/L for men and 349 pmol/L for women (155), which is similar to that of American whites in the National Health and Nutrition Examination Survey (NHANES) III (177), despite an apparent lower intake of vitamin B12 (less than 1.5 ug/day for half the cohort). The plasma vitamin B12 was a significant predictor of the total homocysteine value (155). A cohort of 204 elderly urban Indonesians with an estimated median intake of 3 ug/day had a mean plasma vitamin B12 of 371 pmol/L, and only 8% were below 148 pmol/L (91). The median serum B12 was higher (354–398 pmol/L) in elderly Thais than for the same age group in NHANES III. However, values ranged as low as 24 pmol/L and 7% were under 148 pmol/L, which is similar to U.S. values (137).

VITAMIN B12 DEFICIENCY DUE TO INADEQUATE INTAKE

Daily Requirements

The Recommended Dietary Allowance (RDA) for U.S. adults was set at 2.4 ug/d by the Institute of Medicine (125a) to ensure absorption of 1 ug/d because the average absorption from food is about 50% (75, 151). However, many populations ingest less than 1 ug/d, and may or may not have metabolic or clinical markers of vitamin B12 deficiency. The reticulocyte count rose in six of eight relapsed PA

patients after injection of 0.1 ug of B12 (164). Diets that contained 0.3–0.65 ug/d cured megaloblastic anemia in five Asian Indian patients with extremely severe diet-induced megaloblastic anemia, although the vitamin B12 levels remained low at 80–100 pmol/L (19). It seems reasonable that diets containing at least 0.5 ug/d will prevent megaloblastic anemia, although much less is known about the quantity needed for central nervous system function. In addition, hyperhomocysteinemia is prevalent when such restricted diets are followed (Table 2). The daily requirement also varies with body size.

Dietary Sources of B12

Food B12 content has been estimated by microbiologic and competitive binding assays, both of which are likely adequate for the measurement of vitamin B12 in muscle meats, eggs, and dairy products. The measured B12 content is suspect

TABLE 2 Total homocysteine in vegetarians versus omnivores. Mean total homocysteine (umol/L) (N)

Year and country	Vegans	LOV	Low meat*	Omnivores	p[a]	Reference
1999 Chile		13.5 (25)		9.6 (26)	0.0046	(117)
1999 United States	7.9 (25)			8.0 (20)	NS	(67)
1999 Australia	19.2[a] (18)	15.8[a] (43)	11.6[b] (60)	11.0[b] (18)	<0.05	(112)
2000 Chile		12.4 (48)		8.4 (40)	<0.0001	(116)
2000 Slovak Republic	15.8[a] (32)	13.2[a] (62)		10.2[b] (59)	<0.001	(97)
2001 Germany	15.2[a] (7)	11.0 (34)	11.8 (19)	9.8[b] (44)	<0.05	(74)
2001 Italy	26.9[a] (31)	17.4[a] (14)		11.6[b] (29)	<0.005	(21)
2002 Germany	12.8[a] (29)	10.5[a] (64)		8.7[b] (20)	≤0.05	(129)
2002 Taiwan	11.2 (45)			8.6 (45)	<0.0001	(82)
2002 men United Kingdom		15.1 (46)		11.2 (583)	<0.001	(29)
2002 women United Kingdom		11.5 (92)		8.9 (669)	<0.001	(29)

*Low meat = omnivore with infrequent meat ingestion.

[a,b]Values with superscripts are significantly different.

Abbreviations: LOV, lacto-ovo-vegetarian; NS, not significant; P, probability.

in products of fermentation, such as tempeh, fish sauce, algae extracts, and sea vegetables because they contain more inactive corrinoids than true B12. Table 3 shows vitamin B12 content of a wide variety of foods taken mostly from the United States Department of Agriculture's nutrient database (168). Ruminants and rabbit are much richer sources of B12 than is poultry. Seafood such as clams, oysters, octopus, fish, and fish roe are also high. Information on reptiles is lacking. Condiments such as fermented Thai fish sauce can provide significant B12 in the diet (14). The B12 content of cow's milk is five- to tenfold higher than that of goat, and presumably products made from the former would also be richer (84). The most likely candidates for vegetarian sources of vitamin B12 are tempeh (13, 110), nori (174, 175), and *Chlorella* extracts (94). Bacteria forms vitamin B12 during the manufacture of tempeh, and content varies widely depending on the conditions of fermentation and the type of contaminating bacteria (13, 92, 110). Whether nori can supply bioavailable B12 is more controversial (142). For instance, the mean cell volume (MCV) did not decrease in vegan children who were fed such products. In contrast, small amounts of fish caused decreases in MCV, as expected (45). However, other data suggest B12 in nori is biologically active (175).

It has been suggested and widely quoted that food contaminated with feces might supply enough vitamin B12 to prevent deficiency in poverty-stricken areas (68). However, human feces have been reported to be at most 159 ng/g (72); cow feces, 120 ng/g; chick, 13 ng/g; and rat, 200 ng/g (136). These values may all be overestimates because current assays are not truly specific for B12. The reader will have to decide whether it is reasonable to assume individuals may inadvertently ingest 2–5 g of dried feces per day.

B12 Deficiency in Breast-Fed Infants

The Institute of Medicine's Food and Nutrition Board has set an infant requirement for vitamin B12 of 0.4 ug/d (125a), and the average breast milk B12 concentration is 0.42 ug/L (6). A severe syndrome of megaloblastic anemia and developmental abnormality was described in breast-fed infants of Asian Indian mothers long ago (53), but due to the recent rise of exclusive breast feeding in developed countries, the severely affected vitamin B12–deficient infant is not uncommon worldwide. An alert from the U.S. Centers for Disease Control that was published in its *Mortality and Morbidity Weekly Report* and highlighted in *JAMA* in early 2003 suggested that health care providers should be vigilant for this clinical situation (55). Breast milk can be deficient in vitamin B12 because of a vegan diet, undiagnosed PA, or another malabsorption syndrome in the mother. The long-term neurologic outcome is poor (65). The deficient mothers are frequently clinically and hematologically normal, although elevated methylmalonic acid may be present (118, 123).

Increased urinary and serum methylmalonic acid has been found in breast-fed infants of women who follow macrobiotic or vegan dietary practices (157, 162), with strong inverse correlations between the milk vitamin B12 levels and the infant methylmalonic acid excretions (161). The plasma methylmalonic acid and

TABLE 3 Vitamin B12 content of foods

Food	Unit	B_{12} (ug)	Reference[a]	Food	Unit	B_{12} (ug)	Reference
Beef liver	100 g[a]	83.10	(168)	Clams	100 g	96.60	(168)
Beef (ground)	100 g	2.56	(168)	Oysters	100 g	18.70	(168)
Lamb	100 g	3.03	(168)	Catfish	100 g	2.80	(168)
Goat	100 g	1.19	(168)	Herring	100 g	9.62	(168)
Pork	100 g	0.75	(168)	Tuna (canned)	100 g	2.99	(168)
Rabbit	100 g	8.30	(168)	Fish roe	100 g	10.00	(168)
Opossum	100 g	8.30	(168)	Octopus	100 g	36.00	(168)
Squirrel	100 g	6.50	(168)	Snail	100 g	0.50	(168)
Turkey	100 g	0.37	(168)	Turtle	100 g	1.00	(168)
Chicken	100 g	0.22	(168)	Frog legs	100 g	0.40	(168)
Duck	100 g	0.30	(168)	Shrimp	100 g	1.49	(168)
Pigeon	100 g	0.47	(168)	Crayfish	100 g	2.15	(168)
Emu	100 g	2.20	(168)				(168)
Cow milk fluid (1%)	1 cup (244 g)	1.074	(168)	Tempeh[b]	100 g	0.18–6.30	(13, 110)
Cow milk fluid (whole)	1 cup (244 g)	0.488–1.92	(84)	Fish sauce[b]	15 g	0.285	(14)
Goat milk fluid	1 cup (244 g)	0.195	(84)	Nori[b]	3 g (1 sheet)	2.00	(174)
Cow milk, evaporated	1 cup (244 g)	0.614	(84)	Chlorella tablets[b]	1 g	2.00	(94)
Yogurt (low fat), plain	8 oz. container	1.385	(168)				
Cheese (cheddar)	28.35 g	0.830	(168)				
Egg	1 large (50 g)	0.645	(168)				

[a]100 gm = 3 oz. serving.

[b]Reported B_{12} content probably includes analogues.

homocysteine were stronger predictors of dietary insufficiency than were vitamin B12 values.

Vitamin B12 Deficiency Due to Vegetarianism

The popularity of diets that limit intake of animal products has risen during the past decade. Individuals embrace these diets for religious, philosophical, and especially health reasons. Those who follow vegetarian diets generally are well nourished, healthy, and not plagued with parasites, malabsorption, or protein calorie malnutrition, comorbidities that can confuse the clinical picture of B12 deficiency. A Dutch cohort of children raised in families that followed a macrobiotic diet has identified clinical consequences to chronic B12 deficiency (46). The birth weight of infants was related to the frequency of the mother's consumption of dairy products and fish. The mean vitamin B12 intake in the macrobiotic infants (6–16 months old) was 0.3 ug/day in contrast to a control group of infants at 2.9 ug/day. The breast milk content of B12 was lower than in control mothers (48). The infants had low mean plasma vitamin B12 (149 pmol/L), higher MCV, and slightly lower hematocrit than controls, which indicated that they likely had megaloblastic erythropoiesis even though plasma folates were much higher (47). Plasma methylmalonic acid and total homocysteine were abnormal in 83% of the infants with strong negative correlations between the metabolites and plasma vitamin B12 (157). The data were so convincing that the researchers were able to help the macrobiotic community change the diet to increase intake of fatty fish and dairy products. Yet in a follow-up study of children who had been on the macrobiotic diet until age 6, the mean methylmalonic acid was still approximately twice that of the control children and MCV was still higher. The current median estimated vitamin B12 intake is 1.5 ug/d for the boys and 1.2 ug/d for girls (171). The same cohort was shown to have impairments in fluid intelligence, which correlated with poor vitamin B12 status, and reinforced the concept that adequate vitamin B12 nutrition in early life may be very important (111). In contrast, a study of British lacto-ovo-vegetarian children revealed adequate vitamin B12 intake (2.5 ug/day), largely due to a high intake of dairy products and occasional consumption of fish (125).

Megaloblastic anemia due to dietary deficiency was thought to be rare until the 1970s, when reports, mostly from Great Britain, described cases in Asian Indians and other vegetarians (ably reviewed in Reference 12, and 4, 15, 26, 39, 41, 54, 62, 63, 83, 143, 145, 152). Intake data are sparse, but it appears that the average lacto-ovo-vegetarian consumes <1 ug B12 per day (40, 83). The intake of vitamin B12 in vegetarian children in Boston correlated inversely with urinary methylmalonic acid, and excretion doubled in those who consumed <0.2 ug/day. There was no relationship between serum vitamin B12 values and consumption of sea vegetables or tempeh and miso (119). In general, this research also shows that clinically apparent megaloblastic anemia and neurologic abnormalities due to B12 deficiency are rare in the vegetarian communities.

Total homocysteine concentrations are generally higher in vegetarians than in omnivores, and there has been speculation that this is related to the high prevalence of vascular disease in Asian Indians, which is ironic because one of the proposed benefits of the vegetarian lifestyle is a decreased risk for cardiovascular disease. Table 2 shows the homocysteine values in vegetarians versus omnivore controls in recent investigations, which span the globe. Total homocysteine was not higher in the study from the United States (67) because of high B12 intake in the vegetarians, 2.9 ug/day from fortified meat substitutes. When supplements were included, total B12 intake was 5.9 ug/day. A study from Taiwan (82) showed a difference in intake between 0.42 and 7.1 ug/d for vegans versus omnivores. There are also recent reports of Asian Indians in the United States with elevated plasma total homocysteine, which was related to low plasma vitamin B12 and diets that contained only infrequent intake of poultry or fish (34, 40).

Dietary Vitamin B12 Status in the United States, Canada, and Europe

The estimated vitamin B12 intake in the United States, Canada, and Europe is higher than the Food and Nutrition Board's RDA of 2.4 for adults, 1.5 for older children, and 0.7 for toddlers (125a). Median daily intakes in the United States of 3–4 ug and in Canada 4–7 ug have been reported (125a). The elderly also have a high intake in the United States, Canada, and Germany (80, 138, 150, 176). The mean vitamin B12 levels are remarkably uniform over the white populations of the United States (177), Canada (49), Germany (141), and Britain (20), with younger children usually about 100 pmol higher than older children, and adult means of about 320 pmol/L. Data from NHANES III in the United States show that non-Hispanic whites have the lowest B12 values, followed by Mexican Americans, and the highest concentrations (about 70 pmol higher) are in non-Hispanic blacks (177). Senior Caribbean Hispanics had lower B12 intake and plasma B12 than non-Hispanic whites in a study from Boston (100). The use of B12-supplemented foods may remove the risk of deficiency even for vegetarians in these countries.

GEOGRAPHIC AREAS OF VITAMIN B12 DEFICIENCY

Indian Subcontinent

Vitamin B12 nutrition is problematic in India due both to lactovegetarianism and the expense and scarcity of meat ingestion even in omnivores (reviewed in References 11, 12). Dietary deficiency in India has been associated with megaloblastic anemia and neurologic syndromes. A recent report from New Delhi studied severe megaloblastic anemia with pancytopenia in children age 6 months to 12 years (41). Tremor was present in 11% of the youngest infants. The median vitamin B12 values were extremely low: 43 pmol/L for infants and 31 pmol/L in the mothers. Folate deficiency was less prevalent (41). Vitamin B12 deficiency is also a

major problem in northern Pakistan, where investigators calculated a 95% reference range in a normal population of 107–236 pmol/L, remarkably lower than in the United States (122). Severe megaloblastic anemia was due to vitamin B12 deficiency in 56% of patients, serum folate alone, 8%, and combined deficiency, 20% (122).

Hyperhomocysteinemia may be a modifiable risk factor in Asian Indians who have a high prevalence of cardiovascular disease both in their native country and as immigrants. The mean total homocysteine was 13.3 umol/L in persons from Bangladesh and India living in the United Kingdom as compared to 8.5 umol/L in white British blood donors (36). The mean serum vitamin B12 was 154 pmol/L (half the U.S. mean) in 200 subjects from Pune, India, even though only 38% excluded meat, poultry, fish, and eggs (144). The median total homocysteine was 19.8 umol/L and 77% were greater than 15 umol/L. The mean methylmalonic acid was 490 nmol/L, with 73% higher than 260 nmol/L. Dairy products were consumed daily by 98% of the subjects and eggs were eaten by 92% of the vegetarians. The nonvegetarian diet included little animal food, as only 38% ate animal products more than one time per month; thus B12 nutrition was poor in both vegetarians and omnivores. Intake of mutton was beneficial (144). In New Delhi, mean serum total homocysteine was high in urban slum and nonslum dwellers, 20.8 umol/L and 23.2 umol/L, respectively. Although 84% of the slum dwellers were not vegetarians, their mean daily B12 intake was only 0.75 ug. This was higher than the mean intake of 0.55 ug for nonslum dwellers, of whom 50% were vegetarians (120). Dietary B12 deficiency is probably prevalent in the Himalayas also. The serum B12 value was <150 pmol/L in 17.3% of a survey of villagers (2) and in 49% of pregnant Nepali women (23). Methylmalonic acid and total homocysteine were elevated in 61% and 68% of the latter, but were not associated with anemia.

Middle East

An investigation of Bedouin patients in Israel with anemia or weakness and neurologic symptoms showed that 50% had a vitamin B12 level <118 pmol/L (113), many with macrocytosis. Myelopathy and neuropathy symptoms were prominent in up to one third of the subjects with B12 <118 pmol/L, whereas those with serum B12 >221 pmol/L rarely had such symptoms or signs. Meat consumption was <50 g per week in 41% and 51–100 g in 39% of those with low B12 levels. Those with normal B12 levels ate greater amounts of meat. This population originally herded sheep and camels, but had relocated to an urban area and was living in poverty on bread, vegetables, and canned food (113). Serum vitamin B12 was 20% lower and mean methylmalonic acid doubled in Syrian subjects as compared to Germans, which was likely due to low meat intake in the former (73).

Africa

Until recently, vitamin B12 deficiency was thought to be rare in Africa (114), despite the awareness that many diets were deficient in animal products. Anemic

pregnant Nigerians studied in 1969 ate at most about 18 g of meat per day, which would supply only about 0.4 ug of B12, yet the mean serum vitamin B12 values were unexpectedly high (58). Dietary B12 deficiency and vegetarianism was not seen in the large series of hospitalized patients in Zimbabwe with megaloblastic anemia, and most patients had probable PA (153). The hunter-gatherer diet of the !Kung Bushman in 1971 was rich in meat derived from a wide variety of small and large mammals, and high serum vitamin B12 levels (median of 455 pmol/L for males) were reported from Botswana (115). The median vitamin B12 levels were still adequate, 300–400 pmol/L, in a similar group of Bushman studied in 1994 after they had adopted a Western lifestyle and made substantial dietary changes (43). A longitudinal study from the slopes of Mount Kenya showed that the vitamin B12 intake was inadequate in 44% of toddlers and 86% of school children and was associated with megaloblastic anemia in 4% to 8% of children. The B12 and animal protein intake predicted height in the toddlers at 30 months, and supplemental B12 may have improved linear growth (126). A median vitamin B12 concentration of 205 pmol/L, with median total homocysteine, 15.9 umol/L, was found in adolescent Nigerian girls at a government-sponsored secondary school. The mean serum folate was 15.3 nmol/L. B12 deficiency was likely due to a diet that was devoid of animal food with the exception of dried fish, which could be purchased by the girls as a snack (170). In marked contrast, the diet of Nigerian Fulani pastoralists includes large amounts of meat and dairy products, and estimated dietary intakes of B12 are between 4.7 and 7 ug (64). A detailed investigation of anemic pregnant women in Malawi showed that 33% had serum vitamin B12 less than 148 pmol/L and 16% less than 52 pmol/L. The association between these concentrations and megaloblastic changes in bone marrow samples was linear and statistically significant (169).

Asia

The mean and tenth percentile for plasma vitamin B12 was similar in young Chinese women from Anqing and those in the United States as reported in the NHANES III (147, 177). However, a follow-up study showed that preterm birth was 60% lower among women who had vitamin B12 $\geq$ 258 pmol/L and was nearly fourfold higher among women who had higher homocysteine concentrations preconception (148). The intake of vitamin B12 could be calculated at about 2–5 ug/d in a study of breast milk composition from four regions in China (149). Mean vitamin B12 values were also fairly high (between 313–437 pmol/L) in children eating a lacto-ovo-vegetarian diet in Hong Kong, with an estimated 0.5–1 ug/d intake of vitamin B12 (103). The serum vitamin B12 and plasma total homocysteine values in a group of middle-aged patients and controls in Taiwan were very similar to values seen in the United States, which suggests that vitamin B12 nutrition was adequate (105).

Data from the National University of Singapore Heart Study have shown that plasma vitamin B12 was lower in Indians than in Chinese or Malays but did not

correlate inversely with homocysteine, which was highest in the Indians (81). The mean vitamin B12 concentrations ranged from 269 pmol/L in the Indian subjects to 354 pmol/L in the Malay subjects, and acute myocardial infarction was strongly associated with lower vitamin B12 (127) in an investigation of patients presenting to a hospital in Singapore.

Korean adults had higher fiftieth and tenth percentile plasma vitamin B12 values than values reported in the United States in NHANES III, with a corresponding mean homocysteine value of 10.3 umol/L (104). The mean vitamin B12 values were also higher than in the United States in the Japan Public Health Center–based prospective study in middle-aged men, with estimated intake of 4–6.4 ug/day (86).

Male urban workers in Bangkok had a mean serum vitamin B12 of about the eighty-fifth percentile reported for the United States in NHANES III, possibly due to the ingestion of vitamin-fortified "tonic drinks" (165). Rural women from Northeast Thailand of childbearing age were found to have mean vitamin B12 at the seventy-fifth percentile reported in NHANES III (167). Lactovegetarians from a Buddhist sect in Bangkok were found to have median vitamin B12 concentrations of 80 pmol/L. A previous dietary analysis suggested that the daily vitamin B12 consumption was approximately 0.4 ug/day (166). In another study of Thai vegetarians, the hemoglobin and white blood count were significantly lower in vegetarians whose median B12 value was 149 pmol/L (135). Dietary vitamin B12 deficiency seems infrequent in Asia, except in vegetarians.

Mexico and Central and South America

A series of studies from rural central Mexico from the Collaborative Research Support Program have shown that vitamin B12 deficiency is highly prevalent because of the low intake of animal food products. The mean vitamin B12 level in women was 181–228 pmol/L, roughly only 50% that of Mexican American women of childbearing age reported in NHANES III (22, 177). The anemic women consumed fewer animal products, and anemic lactating women had lower breast milk vitamin B12 content, 285 versus 418 pmol/L. Meat was usually eaten only once a week, although eggs were consumed every other day (22). Preschool and school-aged children from the same community also had very low mean plasma vitamin B12: 140 and 150 pmol/L, respectively. The diet included 20 ml dried cow milk each day, eggs every other day, and chicken once a week at most (8). Children who had higher vitamin B12 concentrations at baseline had a better hemoglobin rise with iron supplements (7). The median vitamin B12 intake of women in another area of rural Mexico was estimated to be 1 ug. Serum B12 in 42% of the population was less than 150 pmol/L, and lower values correlated with lower hematocrit (17). Lactating women from Capulhuac, Mexico, reported a median vitamin B12 intake of 1.5 ug/day, mostly from eggs (172).

The hematologic and vitamin status was compared between two Bari Indian populations from Western Venezuela. Those living in a fertile mountain area had mean serum vitamin B12 values that were in the fiftieth to seventy-fifth percentile for NHANES III in Mexican Americans (52). However, a group that had relocated

to an arid area and consumed virtually no animal protein had a mean serum B12 value of 126 pmol/L. Both populations were infected with *Helicobacter Pylori* and intestinal parasites, which suggests that dietary vitamin B12 is more important than is possible malabsorption in predicting status (52).

The mean plasma vitamin B12 in a group of Guatemalan lactating women was only 75% of the value seen in NHANES III, and 13.4% were <147 pmol/L. Urinary methylmalonic acid excretion was elevated in 12% of the infants and correlated negatively with breast milk intake (35). Breast milk vitamin B12 was lower in the mothers of infants with elevated urinary methylmalonic acid (35). The mean plasma vitamin B12 in school children from Guatemala was approximately the fifth percentile for NHANES III in the United States, and B12 was <162 pmol/L for 11% of the children. The serum methylmalonic acid and total homocysteine were higher in those with B12 <162 pmol/L as compared to >221 pmol/L, which confirms a metabolic deficiency. Most children consumed eggs and small amounts of milk daily and meat only weekly (146).

Median serum vitamin B12 values in pregnant and nonpregnant females and males from seven different countries in Central and South America were low (50% of NHANES III value) (44). The values obtained in pregnant Brazilian women at parturition was very similar 30 years later in a poor population from Sao Paulo, with a median value of 133 pmol/L (66). The cord blood vitamin B12 was highly correlated with maternal B12 values: Cord blood total homocysteine was negatively correlated with maternal vitamin B12 and positively correlated maternal total homocysteine values, which suggests that infants born to mothers with dietary-induced vitamin B12 deficiency may be B12-deficient at birth (66).

TREATMENT AND PREVENTION OF VITAMIN B12 DEFICIENCY

PA is the major cause of severe megaloblastic anemia in the world. The dramatic rise in hematocrit and improvement of neurologic symptoms after vitamin B12 treatment is so specific that assessment of response can be the only diagnostic testing needed. Health care resources should be directed toward supplying high-dose oral (1000 ug) vitamin B12 formulations (99) for treatment of PA rather than toward implementation of expensive diagnostic testing such as Schilling tests, intrinsic factor antibodies, and metabolite assays in countries where money for health care is limited. Women of childbearing age with familial or personal history of autoimmune thyroid disease or PA should be screened for vitamin B12 deficiency or empirically treated with high-dose oral vitamin B12 in order to prevent the tragic occurrence of the vitamin B12-deficient breast-fed infant. Any individual with clinical deficiency who consumes animal products more than weekly should be assumed to have malabsorption and therefore should be treated with high-dose supplements because smaller oral doses have not been shown to correct elevated methylmalonic acid (139). Soymilk and meat substitutes should be fortified and appropriately labeled with vitamin B12 so that vegetarians may ensure an adequate

vitamin B12 intake. Vegetarians (particularly children) should be screened for vitamin B12 deficiency with serum methylmalonic acid assays. Health-conscious vegetarians could also consider screening for hyperhomocysteinemia or using B12 supplements.

New specific methods for assaying vitamin B12 in foodstuffs are urgently needed so that recommendations about possible alternative inexpensive food sources of vitamin B12 can be disseminated. For instance, if it is proven that tempeh, or the algaes nori and chlorella, are reliable sources of B12 nutrition, then they would be an acceptable B12 source for vegetarians and a less expensive alternative to increasing animal protein intake in poverty-stricken areas. Nutritional vitamin B12 deficiency appears less prevalent in Asia, which could possibly be due to a greater exploitation of all forms of seafood and invertebrate and reptile animal foods in those diets, as well as inclusion of fermented soy products, algaes, and fish sauces. An analysis of the B12 content of the diets common in China, Japan, and Southeast Asia using specific methods could provide information for designing low-cost dietary improvements for the B12-deficient populations in South America, India, and Africa. A good example of using locally prepared fish powder to enhance a cereal weaning food in Ghana has been reported and could be a useful model for other areas (102). Another potential public health strategy is intermittent high-dose oral supplements of vitamin B12 dispensed at schools or clinics. Since 1% of an oral dose can be absorbed, the 10 ug available from a 1000 ug tablet taken monthly would probably prevent anemia, although total homocysteine and methylmalonic acid would still be abnormal. This approach should be studied using metabolites to monitor response. Vitamin B12 should be added to iron and folate supplements given to pregnant and lactating women.

AUTHOR NOTE

S.P.S. and R.H.A. hold patents involving the use of assays for methylmalonic acid and total homocysteine in the diagnosis of viamin B12 and folate deficiency as well as patents involving combination high-dose vitamin pills to lower such metabolites. A company has been formed at the University of Colorado to assay total homocysteine and methylmalonic acid.

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