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VITAMIN B_{12} DEFICIENCY IN THE ELDERLY

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ABSTRACT

Vitamin B_{12} deficiency is estimated to affect 10%–15% of people over the age of 60, and the laboratory diagnosis is usually based on low serum vitamin B_{12} levels or elevated serum methylmalonic acid and homocysteine levels. Although elderly people with low vitamin B_{12} status frequently lack the classical signs and symptoms of vitamin B_{12} deficiency, e.g. megaloblastic anemia, precise evaluation and treatment in this population is important. Absorption of crystalline vitamin B_{12} does not decline with advancing age. However, compared with the younger population, absorption of protein-bound vitamin B_{12} is decreased in the elderly, owing to a high prevalence of atrophic gastritis in this age group. Atrophic gastritis results in a low acid-pepsin secretion by the gastric mucosa, which in turn results in a reduced release of free vitamin B_{12} from food proteins. Furthermore, hypochlorhydria in atrophic gastritis results in bacterial overgrowth of the stomach and small intestine, and these bacteria may bind vitamin B_{12} for their own use. The ability to absorb crystalline vitamin B_{12} remains intact in older people with atrophic gastritis. The 1998 recommended daily allowance for vitamin B_{12} is 2.4 μg, but elderly people should try to obtain their vitamin B_{12} from either supplements or fortified foods (e.g. fortified ready-to-eat breakfast cereals) to ensure adequate absorption from the gastrointestinal tract. Because the American food supply is now being fortified with folic acid, concern is increasing about neurologic exacerbation in individuals with marginal vitamin B_{12} status and high-dose folate intake.

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FUNCTIONS OF VITAMIN B_{12}

Vitamin B_{12} is a biologically active corrinoid, a group of cobalt-containing compounds with macrocyclic pyrrol rings (71). Vitamin B_{12} functions as a cofactor for two enzymes, methionine synthase and L-methylmalonyl coenzyme A (CoA) mutase. Methionine synthase requires methylcobalamin for the methyl transfer from methyltetrahydrofolate to homocysteine to form methionine tetrahydrofolate. L-Methylmalonyl–CoA mutase requires adenosylcobalamin to convert L-methylmalonyl–CoA to succinyl-CoA in an isomerization reaction. An inadequate supply of vitamin B_{12} results in neuropathy, megaloblastic anemia, and gastrointestinal symptoms.

ABSORPTION, METABOLISM, STORAGE, AND EXCRETION OF VITAMIN B_{12}

Absorption, Metabolism, and Storage

There are two pathways for absorption of vitamin B_{12}, intrinsic factor associated and passive diffusion. The first pathway is an active process, which requires an

intact stomach, intrinsic factor, pancreatic enzymes, and normally functioning terminal ileum. Free vitamin B_{12} must be released from dietary protein in the stomach by the action of acid and pepsin. The released free vitamin B_{12} then binds to R protein in the stomach. R protein is a haptocorrin found in saliva, gastric juice, bile, intestinal juice, and serum. R protein is degraded by pancreatic enzymes in the alkaline environment of the small intestine, thus freeing vitamin B_{12} from R protein to form the vitamin B_{12}–intrinsic factor complex. Intrinsic factor is a 60-kDa glycoprotein that is secreted by gastric parietal cells after stimulation by food. Once formed, the vitamin B_{12}–intrinsic factor complex is stable and proceeds to the ileum, where the vitamin B_{12}–intrinsic factor complex is attached to specific membrane receptors of the ileum and then is absorbed by phagocytosis (124). This intrinsic factor–related process has a limited capacity for absorbing vitamin B_{12}, with a maximum of 3 μg at one meal. However, when large quantities of vitamin B_{12} are ingested, significant amounts of the vitamin can be absorbed by passive diffusion. The rate of absorption by the passive process is 1% of the ingested amount of vitamin B_{12} (18). Adams et al (4) reported fractional absorption estimates of radiolabeled cyanocobalamin when given at different doses: 50% of a 1-μg dose is retained, 20% of a 5-μg dose is retained, and just over 5% of a 25-μg dose is retained. Thus, although total amount of vitamin B_{12} absorption increases with increasing intake, the fractional absorption decreases as the oral dose is increased (35).

There are three circulating plasma vitamin B_{12} binding proteins: transcobalamin (TC) I, TC II, and TC III. TC I binds to approximately 80% of the circulating vitamin B_{12}, whereas TC II binds to less than 20% of circulating vitamin B_{12}. However, vitamin B_{12} enters cells throughout the body mainly bound to TC II, which is a protein synthesized in the liver. TC II binds to 7%–20% of the endogenous cobalamin (48, 65) and mediates 33%–99% of the total plasma vitamin B_{12} clearance (9, 64). TC I and TC III are R proteins (57), which belong immunologically to the same class of vitamin B_{12} binding glycoproteins found in secretions and granulocytes. Although TC I binds 80%–90% of the endogenous cobalamin, TC I mediates less than 1% of the total cellular uptake of vitamin B_{12} from plasma (8, 9, 50, 57, 67, 81, 122, 123).

Estimates of total-body vitamin B_{12} storage range between 2.0 and 3.9 mg (3, 5, 58, 112), and the liver is the main site for storage. In adults, the average vitamin B_{12} content of the liver is approximately 1.0 μg/g of tissue, and the liver holds about half of the total-body storage (3, 35).

Enterohepatic Circulation of Vitamin B_{12}

Vitamin B_{12} is secreted into the bile at the rate of 1.4–9.0 μg daily. Two thirds of the secreted vitamin B_{12} in bile is reabsorbed by the intestine (58, 113). el Kholty et al (45) demonstrated that the mean secretion of vitamin B_{12} into

bile averages 1.0 ± 0.44 nmol/day (1.4 μg/day) in eight cholecystectomized patients, which represents 55% of total corrinoids. Removal of potentially hazardous vitamin B_{12} analogues might be one of the functions of the enterohepatic circulation (14, 63). The average loss of biliary vitamin B_{12} in the stool is about 0.4 μg/day. Although both Green et al (60) and Teo et al (139) suggested that bile enhances vitamin B_{12} absorption, the enterohepatic circulation of vitamin B_{12} is dependent on the presence of intrinsic factor. In the absence of intrinsic factor, all the vitamin B_{12} from the bile is excreted into the stool instead of being recirculated. Individuals with pernicious anemia (complete absence of intrinsic factor) develop vitamin B_{12} deficiency rapidly, in approximately 1–3 years, compared with those whose vitamin B_{12} deficiency stems from other causes (13, 50, 84).

Excretion of Vitamin B_{12}

Loss of vitamin B_{12} occurs mostly through the feces. Sources of fecal vitamin B_{12} are unabsorbed vitamin B_{12} from food or bile, desquamated cells, gastric and intestinal secretions, and vitamin B_{12} synthesized by intestinal bacteria. When present in amounts in excess of the plasma vitamin B_{12} binding capacity (e.g. after an injection of vitamin B_{12}), vitamin B_{12} is also lost through urine. Other routes of vitamin B_{12} loss are through skin and other body secretions. The amount of vitamin B_{12} excreted from the body (turnover rate) is fixed at 0.1%–0.2% of total body stores daily, regardless of the size of the pool (13, 20, 21, 74, 111, 112). Although the rate of vitamin B_{12} excretion is not directly proportional to intake, increased intake of vitamin B_{12} results in greater liver storage and, thus, increased excretion.

BIOAVAILABILITY OF VITAMIN B_{12} FROM DIFFERENT FOOD SOURCES

In healthy adults, the percentage of vitamin B_{12} absorbed from eggs is 24%–36% (41), from trout 25%–47% (42), and from chicken, mutton, and liver 60%, 65%, and 9%, respectively (40, 74). The bioavailability of vitamin B_{12} from liver is low because its content of vitamin B_{12} is high. Studies on the bioavailability of vitamin B_{12} from dairy products or red meat other than mutton and liver have not been reported. Heyssel et al (74) studied the absorption rate of vitamin B_{12} in men with pernicious anemia and men with normal gastric function. In those with pernicious anemia, a disorder of intrinsic factor deficiency, naturally occurring vitamin B_{12} and low-dose (less than 5 μg) crystalline vitamin B_{12} were not absorbed at all. In subjects with normal gastric function, the absorption rate of naturally occurring vitamin B_{12} was 50% and that of low-dose crystalline vitamin B_{12} was 60%. High-dose (larger than 500 μg) crystalline vitamin

B_{12} absorption was the same in both groups, 1% (18). When high doses of crystalline vitamin B_{12} were given with food, the rate of absorption was 0.5% and less than 0.5% in those with normal gastric function and pernicious anemia, respectively.

FOOD SOURCES OF VITAMIN B_{12} IN THE ELDERLY

Animal-origin food is the only natural food source of vitamin B_{12}. Plant foods do not provide it unless the plant was exposed to vitamin B_{12}–producing bacteria, contaminated with vitamin B_{12}–containing substances (soil, insect parts, etc), or fortified with vitamin B_{12} (e.g. fortified ready-to-eat breakfast cereals). Foods high in vitamin B_{12} are dairy products, meat, liver, fish, eggs, and shellfish. For adults in America, mixed foods (including sandwiches) composed mainly of meat, fish, or poultry are the most common sources of dietary vitamin B_{12} (145b). The second most common source for women is milk and milk drinks and for men is beef. Other foods that are rich in vitamin B_{12} (e.g. shellfish, liver, fish) are not eaten regularly in the United States.

Because atrophic gastritis with decreased acid pepsin production is prevalent in the elderly, absorption of food-bound vitamin B_{12} is lower in older than in younger, healthier people. The bioavailability of crystalline vitamin B_{12}, however, is not affected by atrophic gastritis. Fortified cereals contribute 4.7% of the total intake of vitamin B_{12} in all adult men and 8.2% in all adult women. In men and women aged 51–70 years, the contribution is 7.8% and 10.3%, respectively, whereas for those over 71 years old, fortified cereals contribute about 11.5% of the total vitamin intake (A Moshfegh, personal communication). These data show that fortified foods contribute a larger proportion of vitamin B_{12} to older than to younger adults. Fortifying food with cyanocobalamin should be evaluated as a means of supplying adequate amounts of vitamin B_{12} to the elderly, whether or not they have malabsorption of food-bound vitamin B_{12} due to atrophic gastritis. Such an evaluation should include the feasibility and potential benefits and/or adverse effects of vitamin B_{12} fortification, the stability of the fortificant, the identification of any degradation products, and the bioavailability in normal subjects and in those with atrophic gastritis.

Milk is the most important source of vitamin B_{12} for lactovegetarians because it contains 0.4 μg/100 ml (0.9 μg/cup). Stewart et al (134) reported that vitamin B_{12} content reduced by about 50% in milk boiled for 10 min. In reconstituted evaporated milk, the content of vitamin B_{12} is about 25% that of fluid whole milk (145a). Thus, cooking losses may seriously decrease vitamin B_{12} intake in lactovegetarians (134), and fresh, pasteurized fluid milk is recommended to such individuals.

PREVALENCE OF VITAMIN B_{12} DEFICIENCY IN THE ELDERLY

Factors Contributing to Declining Vitamin B_{12} Status with Aging

PERNICIOUS ANEMIA Pernicious anemia associated with gastric atrophy is the most common cause of clinically apparent vitamin B_{12} deficiency in North American and European populations. Pernicious anemia is the end stage of autoimmune gastritis (type A chronic atrophic gastritis or gastric atrophy) in which both the fundus and body of the stomach are involved. The body and fundus of the stomach contain acid-secreting parietal cells and pepsinogen-secreting zymogenic cells. In pernicious anemia, parietal cell autoantibodies directed toward H^+/K^+-ATPase cause loss of gastric parietal cells. Progressive destruction of parietal cells from the gastric mucosa leads to impairment of intrinsic factor production. In addition, blocking antibodies in the gastric juice can bind to the vitamin B_{12} binding site of intrinsic factor to prevent the formation of the vitamin B_{12}–intrinsic factor complex. Thus, in pernicious anemia, vitamin B_{12} deficiency develops by several mechanisms (141). Achlorhydria, low serum pepsinogen I concentrations, and high serum gastrin concentrations caused by hyperplasia of gastrin-producing cells are found in type A gastritis. The mean age at diagnosis of pernicious anemia is 60 years old, and the female-to-male ratio is approximately 1:5. In Caucasians, the prevalence of the disease rises with increasing age, peaking after age 65 (35). In a recent study (28), of a group of free-living individuals over 60 years old, 1.9% had undiagnosed pernicious anemia. The study by Krasinski et al (90) showed a 2.9% prevalence rate of intrinsic factor antibody positivity among physically healthy Caucasians older than 60 years, which matches the estimate of Carmel (28). The prevalence rates for women are higher than for men, and black and white women show higher prevalence of pernicious anemia compared with Latin Americans and Asians. In previous studies, blacks with pernicious anemia had a higher prevalence of anti-intrinsic factor antibody than did whites (27, 119). Also, an earlier onset of pernicious anemia has been reported among blacks and Hispanics. The mean age of presentation among black women is approximately 54 years, and among Hispanics it is approximately 58 years (32, 33, 77). The risk of gastric carcinoma is high in those with pernicious anemia (threefold increased risk), and gastric carcinoid tumors are also prevalent (13-fold proportionate excess of carcinoid tumors among patients with pernicious anemia) (78).

Approximately 20% of the relatives of each patient with pernicious anemia also have pernicious anemia (141), which suggests a genetic predisposition to it. Serum autoantibodies to gastric parietal cells are found in approximately

90% of patients with pernicious anemia. These antibodies are demonstrated in approximately 30% of nonanemic first-degree relatives of patients with pernicious anemia and in patients with other autoimmune endocrinopathies. Also, there is an age-related increase in the prevalence of parietal cell autoantibodies: 2.5% in the third decade compared with 9.6% in the eighth decade (136, 141). Circulating intrinsic factor antibodies are more specific than are parietal cell antibodies and are almost diagnostic of type A gastritis (pernicious anemia) (27, 141).

ATROPHIC GASTRITIS AND FOOD-BOUND VITAMIN B_{12} MALABSORPTION Type B chronic atrophic gastritis involves primarily the gastric antrum and is related to *Helicobacter pylori* infection. The gastric antrum is initially affected, but later on the gastritis spreads to the body of the stomach, resulting in a patchy gastritis. Subclinical vitamin B_{12} deficiency with aging is due mainly to type B atrophic gastritis accompanied by low acid-pepsin production and food-bound vitamin B_{12} malabsorption. Krasinski et al (90) reported the prevalence of atrophic gastritis to be 30% in a Caucasian group over 60 years old living on the east coast of the United States. However, lower estimates (9%) have been reported from the midwest (79). A decrease in gastric acidity leads to reduced release of free vitamin B_{12} from food protein (43, 44, 106). Also, hypochlorhydria causes intestinal bacterial overgrowth, which interferes with vitamin B_{12} absorption. Therefore, malabsorption of protein-bound vitamin B_{12} occurs by both mechanisms in individuals with atrophic gastritis and results in a decline in vitamin B_{12} status (90, 116, 138). However, the absorption rate of crystalline vitamin B_{12} does not decrease in type B atrophic gastritis, as intrinsic factor continues to be produced in sufficient amounts (43, 98).

There are contradictory data in the literature on the effect of type B atrophic gastritis on vitamin B_{12} status in the elderly. van Asselt et al (146) found no significant difference in vitamin B_{12} absorption (free or protein bound) between subjects younger than 64 years (median age, 57 years) and those 65 years and older (median age, 75 years). These authors could not explain the observation of an age-related lowering in plasma vitamin B_{12} values either by the aging process or by the presence of mild or moderate atrophic gastritis. In contrast, Scarlet et al (119a) demonstrated that a reduction with age in dietary vitamin B_{12} absorption was related to elevated serum gastrin levels, which indicates hypochlorhydria. Miller et al (101) studied patients (median age, 61 years) with low vitamin B_{12} values and found that elevated serum gastrin levels were closely associated with poor absorption (less than 12% of absorption) of food-bound vitamin B_{12}. Among a control group with normal serum vitamin B_{12} levels [range 125–284 pmol/liter (170–385 pg/ml)], only 21% had poor absorption of food-bound vitamin B_{12}.

Chronic atrophic gastritis is a precancerous lesion (128). Progressive intestinal metaplasia of gastric mucosa occurs in atrophic gastritis, which develops into an intestinal type gastric carcinoma. Although the risk of gastric carcinoma is increased threefold in cases of pernicious anemia with type A atrophic gastritis (78), the total number of gastric cancer cases is much higher in type B atrophic gastritis, because type B chronic atrophic gastritis associated with *H. pylori* infection is a much more prevalent condition.

Alteration with aging in the functional and structural integrity of the vitamin B_{12} binding proteins resulting in compromised TC II–B_{12} delivery system has also been suggested to be a factor in reducing vitamin B_{12} status in the body (95).

Prevalence of Vitamin B_{12} Deficiency in the Elderly

Serum vitamin B_{12} levels decrease with age, and serum methylmalonic acid concentrations increase with age. These findings reflect a decline in vitamin B_{12} status in the elderly. The increased prevalence of vitamin B_{12} deficiency in the elderly is caused by many factors. As previously discussed, these factors include the presence of pernicious anemia (type A atrophic gastritis) and type B atrophic gastritis. The prevalence of both conditions increases with age. The published prevalence of subnormal vitamin B_{12} concentration in the elderly ranges from 3.0% to 40.5%, depending on the diagnostic criteria used (15, 16, 19, 22, 29, 37, 39, 46, 47, 54, 55, 62, 69, 83, 95, 96, 105, 109, 147, 148).

Previously used standard cutoff points (lowest limits of the normal range) for serum cobalamin level (e.g. 150 pmol/liter, 200 pg/ml) are probably too low and underestimate the frequency of true vitamin B_{12} deficiency in the population (10, 29, 93, 100, 109, 148). In the Framingham study, with a cutoff value for serum cobalamin of 258 pmol/liter (350 pg/ml), the prevalence rate of cobalamin deficiency in a free-living population aged 67–96 years was approximately 12% (93). In a Denver elderly outpatient group, using elevated serum metabolites (methylmalonic acid, homocysteine) in addition to a low or low normal serum cobalamin level (cutoff value of 300 pg/ml), the prevalence was 14.5% (109). Using a serum vitamin B_{12} cutoff level of below 220 pmol/liter (300 pg/ml) and elevated serum levels of methylmalonic acid and/or homocysteine to more than three standard deviations (SDs), the prevalence rate of vitamin B_{12} deficiency was 14.5% among elderly outpatients (mean age, 80 years; range, 65–99 years) (109). In the same group, 56% of patients with low normal serum vitamin B_{12} levels (between 150 and 220 pmol/liter, 201–300 pg/ml) also had elevated methylmalonic acid and/or homocysteine levels to more than three SDs, as compared with 62% of patients with definite low serum cobalamin levels (lower than 150 pmol/liter, 200 pg/ml). In the Framingham Study (93), a group aged 67–96 years and a healthy younger control group ($<$65 years) were

compared: 40.5% of the elderly group had serum vitamin B_{12} levels lower than 258 pmol/liter (350 pg/ml). By using this cutoff value for serum vitamin B_{12} (258 pmol/liter, 350 pg/ml), more than 15% of subjects had elevated methylmalonic acid concentrations (more than three SDs above the mean), whereas less than 10% of subjects above this cutoff did. In the elderly group, 5.3% had vitamin B_{12} values lower than 148 pmol/liter (200 pg/ml) (93).

Herbert (72) measured holotranscobalamin II (vitamin B_{12} bound to TC II) as an indicator of early vitamin B_{12} deficiency and showed poor vitamin B_{12} status in 35% of elderly people aged 65–95 years (see below). In a longitudinal study over a four-year period (68), vitamin B_{12} levels were found to decrease significantly in elderly European women but not in elderly European men. The number of subjects at high risk for vitamin B_{12} deficiency using blood cutoff values below 111 pmol/liter (150 pg/ml) increased from 2.7% at baseline to 7.3% after 4 years of study. However, in a cross-sectional Boston Nutritional Status Survey (114), no age-related changes in vitamin B_{12} status were found. In the Boston Nutritional Status Survey, among free-living subjects aged 60 to more than 90 years (114), the median dietary intake of vitamin B_{12} was 3.4 μg for males and 2.6 μg for females. These values were higher than the 1998 recommended daily allowance (RDA) of 2.4 μg. The median plasma vitamin B_{12} concentration in males who were not taking supplements was 286 pmol/liter (388 pg/ml), and the median plasma vitamin B_{12} concentration for unsupplemented females was 272 pmol/liter (369 pg/ml). For institutionalized subjects, the total median dietary vitamin B_{12} intake also was adequate (4.3 μg and 3.7 μg for males and females, respectively), as defined by the RDA. Vitamin supplements were used in 20% of males and 23% of females. Institutionalized males showed a slightly higher median plasma vitamin B_{12} value than did free-living males. However, institutionalized females had a lower median plasma value than did free-living females. Among both institutionalized males and females, it is notable that those receiving the highest level of skilled nursing care had the highest median values for plasma vitamin B_{12}. Males receiving the least amount of institutionalized care had lower plasma vitamin B_{12} levels. Vitamin B_{12} supplement users had higher median plasma values of vitamin B_{12} compared with nonusers. For both genders, plasma vitamin B_{12} levels increased with increasing doses of supplemental vitamin B_{12}.

In a European study (83) comparing vitamin B_{12} status between healthy elderly subjects aged 65–88 years (median age, 76 years) and elderly hospitalized patients aged 61–97 years (median age, 79 years), the prevalence of vitamin B_{12} deficiency using a serum cutoff value of 103 pmol/liter (140 pg/ml) was 6% and 5%, respectively. However, serum methylmalonic acid (normal range, 62–247 nmol/liter) was elevated in 30% and 51% of healthy elderly subjects and elderly hospitalized patients, respectively. Although the intake of vitamin B_{12} by institutionalized elderly subjects is sometimes higher than that of

free-living elderly, there is a tendency toward an increased prevalence rate of vitamin B_{12} deficiency in the institutionalized group, possibly as a result of a higher prevalence of atrophic gastritis.

DIFFERENCES BY RACE Although there are studies that show an earlier age of onset of pernicious anemia in African Americans, especially women (28, 77, 141), in general African Americans show higher concentrations of serum vitamin B_{12} compared with either white American or Africans (24, 52, 91, 119).

OTHER CAUSES AND EFFECTS OF VITAMIN B_{12} DEFICIENCY IN THE ELDERLY

Inadequate vitamin B_{12} dietary intake is not a frequent condition in the elderly. As mentioned above, the most frequent cause of poor vitamin B_{12} status in the elderly is probably malabsorption of food-bound vitamin B_{12}, although the extent of this problem has not been precisely defined. Reduced gastric acid production due to type B atrophic gastritis combined with bacterial overgrowth is the underlying mechanism of malabsorption of food-bound vitamin B_{12} in the elderly. Acid-reducing drugs also decrease the release from food protein of free vitamin B_{12} (115, 133). Type A atrophic gastritis (pernicious anemia) and gastrectomy cause deficient intrinsic factor, leading to vitamin B_{12} malabsorption. Other, infrequent causes of vitamin B_{12} malabsorption in the elderly are pancreatic insufficiency, terminal ileal disease, lymphoma, radiation enteritis, intestinal tuberculosis, infestation with *Diphyllobothrium latum*, severe celiac disease, and tropical sprue.

Inhalation of the anesthetic nitrous oxide can produce many of the clinical features of acute vitamin B_{12} deficiency by inactivation of the vitamin, resulting in acute megaloblastic anemia and central nervous system damage. Nitrous oxide inhibits both of the cobalamin-dependent enzymes, methionine synthase and L-methylmalonyl–CoA mutase (118). Because nitrous oxide is commonly used for surgery, in an elderly person, vitamin B_{12} deficiency should be ruled out before using this drug. Furthermore, nitrous oxide–induced vitamin B_{12} deficiency should be considered in cases of postoperative neuropathy (12, 49, 53, 76, 87, 89, 99, 120, 121).

CLINICAL FINDINGS OF VITAMIN B_{12} DEFICIENCY IN THE ELDERLY

Neurologic Effects of Deficiency

In the past, neurologic complications were thought to occur at a later stage of vitamin B_{12} deficiency than hematologic changes, but recent reports indicate that neurologic changes can occur in the absence of any hematologic abnormalities.

Neurologic complications are found in 75%–90% of individuals with clinically apparent vitamin B_{12} deficiency. In 25%–33% of patients with neurologic symptoms, the only clinical manifestation is neuropathy (25, 70, 92). The occurrence of neurologic findings due to vitamin B_{12} deficiency is inversely correlated with the degree of anemia, i.e. subjects with severe anemia show fewer or no neurologic manifestations and vice versa (70, 118).

Healton et al (70) showed that patients usually develop neurologic symptoms in their seventh decade or later. Only 20% of patients with neurologic symptoms become symptomatic before age 50.

Cobalamin deficiency of the nervous system is a progressive disorder, which is manifested by abnormalities of the spinal cord, peripheral nerves, optic nerves, and cerebrum. In 33% of patients, there are sensory disturbances in the extremities (paresthesia or numbness) alone. Motor disturbances alone, especially gait ataxia, are present in 9% of cases. Cognitive impairment may occur, ranging from loss of concentration to memory loss, disorientation, and frank dementia, with or without mood changes. Anosmia, fecal and urinary incontinence, leg weakness, impaired manual dexterity, and impotence are less frequent symptoms. Rare symptoms are orthostatic lightheadedness, diminished taste, paranoid psychosis, and diminished visual acuity (70).

Myelopathy alone is present in 12% of cases, whereas combined neuropathy and myelopathy are present in 41% of cases. Bilateral cerebral dysfunction is found in 8.1% of patients with neurologic symptoms, which suggests involvement of cortical neurons or the adjacent white matter. Cognitive syndromes, such as dementia, hallucinations, frank psychosis, paranoia, depression, violent behavior, and changes in personality are not frequent, but vitamin B_{12} deficiency should be considered as a possible cause of these symptoms (61, 70, 118, 135, 149). In 0.5% of cases, visual impairment was found, which might be related to optic atrophy and retrobulbar neuritis or pseudotumor cerebri (130). Depending on the duration of symptoms, neurologic complications of vitamin B_{12} deficiency may or may not be reversible following treatment (the longer the delay before treatment, the less likely recovery).

Hematologic Effects of Deficiency

Megaloblastic anemia is a classical finding of vitamin B_{12} deficiency. However, recent studies have demonstrated that subjects with vitamin B_{12} deficiency often lack anemia and macrocytosis, and that there is a dissociation between the neurological and the hematological manifestations (2, 25, 26, 30, 34, 39, 85, 86, 92, 118).

The hematologic effects of vitamin B_{12} deficiency are indistinguishable from those of folate deficiency. These include pallor of skin and other common symptoms of anemia of gradual onset, such as weakness, tiredness, syncope, headache, shortness of breath, and palpitations. As in folate deficiency, the

underlying mechanism of anemia is defective DNA synthesis in rapidly dividing cells of the bone marrow. This results in a megaloblastic change, with the production of immature large red cells (macrocytosis). This leads to an increase in the red cell distribution width and to an elevated mean cell volume. Oval macrocytosis and other abnormally shaped red cells are present in blood. Typically, as with folate deficiency, the appearance of hypersegmentation of polymorphonuclear leukocytes precedes the occurrence of macrocytosis. There is usually some degree of neutropenia and thrombocytopenia due to the fact that all rapidly dividing bone marrow cells are affected. The hematologic complications of vitamin B_{12} deficiency are completely reversed by treatment with vitamin B_{12}.

Gastrointestinal Effects of Deficiency

Gastrointestinal signs and symptoms of vitamin B_{12} deficiency occur in 26% of cases, as described by Healton et al (70). These include sore tongue, stomatitis, mucosal ulceration, appetite loss, flatulence, and constipation or diarrhea (70). Appetite loss, excess gas, and diarrhea are probably related to the underlying gastric disorder (i.e. gastric atrophy) in pernicious anemia. Gastrointestinal symptoms may occur in the absence of symptomatic anemia or macrocytosis (51).

DIAGNOSIS OF VITAMIN B_{12} DEFICIENCY

Indicators of Hematologic Status

Hematologic indices are the simplest way to diagnose megaloblastic anemia, a classical finding of vitamin B_{12} deficiency. Hemoglobin, hematocrit, red blood cell count, and mean corpuscular volume (66) are all useful tests. However, the response time of these indices is slow because of the 120-day red blood cell survival time. Therefore, these indices alone are not sufficient to diagnose vitamin B_{12} deficiency in the early stage. Hypersegmented neutrophils appear before the development of macrocytosis (140); however, the sensitivity of this finding has recently been questioned (31). The reticulocyte count is a useful measurement of hematologic response to therapeutic vitamin B_{12} administration, as the increase in the reticulocyte count is apparent within 48 h of vitamin B_{12} administration and reaches a peak at 5–8 days.

Serum or Plasma Vitamin B_{12} Levels

The concentration of vitamin B_{12} in the serum or plasma reflects the vitamin B_{12} intake and body stores. For adults, the lower limit of serum vitamin B_{12} is approximately 120–180 pmol/liter (170–250 pg/ml). However, waiting until serum vitamin B_{12} levels reach a low before diagnosing B_{12} deficiency may

delay diagnosis in some cases, because serum values are maintained at the expense of vitamin B_{12} tissue stores. Thus, a serum concentration above the classical cutoff value for defining vitamin B_{12} deficiency does not always mean adequate vitamin B_{12} status. On the other hand, a value below the classical cutoff value does define long-term depletion (17). It has been suggested that the cutoff level for defining normal vitamin B_{12} status might be as high as 300 pg/ml or above (148). Lindenbaum et al (93) showed that 40.5% of a healthy elderly group had serum vitamin B_{12} levels lower than 258 pmol/liter (350 pg/ml) and 15% of those had elevated levels of serum methylmalonic acid. Among elderly patients whose vitamin B_{12} level were $\leq$150 pmol/liter (200 pg/ml), more than 40% had elevated serum methylmalonic acid levels.

Serum Methylmalonic Acid

The normal range of the concentration of serum methylmalonic acid as defined by the mean plus or minus two SDs of a normal adult population is 73–271 nmol/liter (109). When the vitamin B_{12} supply is short, the concentration of serum methylmalonic acid rises. Elevation of serum methylmalonic acid levels may also be caused by renal failure or intravascular volume depletion. Borderline elevations in serum methylmalonic acid levels will not respond to cobalamin therapy in the presence of renal failure (103), although Lindenbaum et al (93) reported that moderate renal dysfunction in the absence of renal failure did not affect methylmalonic acid values as strongly as did inadequate vitamin B_{12} status. Methylmalonic acid values tend to rise in the elderly (82), which appears to reflect inadequate vitamin B_{12} status. As elevated serum methylmalonic acid levels represent a metabolic change that is highly specific to deficiency of vitamin B_{12}, the serum methylmalonic acid concentration is the current preferred indicator of vitamin B_{12} status (7, 61, 82, 104, 117).

Urinary methylmalonic acid excretion is another indicator of vitamin B_{12} deficiency (36, 75, 107, 108, 110), but this measurement is cumbersome compared with the measurement in serum. If a random instead of a 24-h collected urine sample is used, urine methylmalonic acid should be expressed in terms of the creatinine concentration (108). Also, urine methylmalonic acid is influenced by food intake (120), which limits its usefulness.

Serum Homocysteine Concentration

Serum homocysteine levels show a strong inverse association with folate plasma levels, but there is also an inverse association (albeit weaker) with vitamin B_{12} and B_6 plasma levels. Inadequate plasma concentrations of one or more of the above three B vitamins appear to account for 67% of cases of high homocysteine levels (more than 14 pmol/liter) in an elderly population. Because hyperhomocysteinemia is also observed in renal insufficiency or hypovolemia,

serum creatinine is useful for interpretation. Because elevated serum homocysteine concentrations are not specific for vitamin B_{12} deficiency, it is of limited usefulness for evaluation of vitamin B_{12} status. (7, 61, 88, 94, 117, 127, 129, 137).

Other Metabolites

Excretion of formiminoglutamic acid in the urine after oral loading of histidine (88) and serum concentrations of propionate and 2-methylcitrate (11) indicate deficient vitamin B_{12} status. Because formiminoglutamic acid excretion is also increased in folate deficiency, this test lacks specificity for the diagnosis of vitamin B_{12} deficiency. Elevation of serum propionate, a metabolic precursor of methylmalonate, and elevation of serum 2-methylcitrate, which is converted from propionate, are also present in vitamin B_{12} deficiency. However, the measurement of either propionate or methylcitrate has no advantage over methylmalonic acid for the diagnosis of vitamin B_{12} deficiency.

Holotranscobalamin II

Among the three plasma vitamin B_{12} binding proteins, TC II is responsible for receptor-mediated uptake of vitamin B_{12} into cells. TC II is synthesized by the liver and binds only a small fraction of plasma vitamin B_{12} (7%–20%) to form the transcobalamin-vitamin B_{12} complex. This fraction, termed holotranscobalamin II, may be a good indicator of vitamin B_{12} status. Methods to measure TC II have been described (73), and the assay has been used as a screen to detect early stages of low vitamin B_{12} status (56, 59, 72, 95). This assay is currently considered unproven for routine clinical use.

TREATMENT AND DISCUSSION

Specific Therapy Related to the Underlying Disorder

In cases of vitamin B_{12} deficiency due to a correctable underlying dietary deficiency or a treatable disease, the intervention should target the condition (e.g. eradication of parasitic infestation, antibiotics for bacterial overgrowth, treatment of terminal ileal disease, etc).

Replacement Therapy

In pernicious anemia, vitamin B_{12} should be given as intramuscular injections *or* high-dose oral supplements (6). Intramuscular injections of 100–1000 μg of cyanocobalamin for 5 days and 100–1000 μg of cyanocobalamin each month thereafter is a sufficient protocol for treating pernicious anemia. However, a 1-mg daily oral dose can substitute adequately for parenteral therapy, because 1% of ingested cyanocobalamin may be absorbed by passive diffusion, yielding by 10 μg/day (18, 102).

Prevention of Vitamin B_{12} Deficiency in the Elderly

The Food and Nutrition Board recently recommended that the RDA for vitamin B_{12} for adults of all ages be set at 2.4 μg, which is above the previously recommended 2.0 μg/day of the 1989 RDA. The recent fortification of flour with folic acid raises the potential that elderly people will be at an increased risk for developing undiagnosed vitamin B_{12} deficiency, because the higher levels of dietary folate could eliminate the hematologic signs of vitamin B_{12} deficiency and result in a slow progression of neurological signs and symptoms (53a). This is an especially important issue because, as stated before, the reversibility of the neurologic complications of vitamin B_{12} deficiency depends on the duration of delay before treatment is initiated (i.e. the longer the delay before treatment, the less likely it can be reversed). Because of this, the Food and Nutrition Board has advised that elderly people receive their vitamin B_{12} by eating fortified foods (e.g. cereals) and/or vitamin supplements, because the absorption of vitamin B_{12} in the crystalline form is not affected by the presence of atrophic gastritis, which is prevalent in the elderly.

In addition, Herbert (72) proposed periodic screening of elderly people in order to detect early stages of vitamin B_{12} deficiency. For purposes of such screening, serum methylmalonate and/or holotranscobalamin II might be useful. Other indices are not completely suitable: Homocysteine is not specific, hematologic indices may be normal in the presence of tissue vitamin deficiency, and serum vitamin B_{12} levels may be in the low normal range despite tissue deficiency.

According to recent studies, elevated serum total homocysteine is an independent risk factor for all forms of arteriosclerotic vascular disease (23, 80, 97, 125, 126, 131, 132, 142). Although folate deficiency is a far more common cause of elevated homocysteine levels than are vitamin B_{12} and vitamin B_6 deficiencies, an elevated homocysteine value in an old person should not be considered due to folate deficiency alone (38, 125, 127, 144, 145). Because elderly people may have elevated homocysteine levels due to vitamin B_{12} deficiency, lowering serum total homocysteine levels to reduce the high incidence of vascular disease among the elderly by supplying adequate amounts of all three vitamins may become an important public health issue (104, 143, 145).

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