CLINICAL PRACTICE

Vitamin B_{12} Deficiency

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 57-year-old woman reports increasing symptoms of painful paresthesias in both legs for the past 18 months. Physical examination reveals impaired position sense and vibration sense. The serum vitamin B_{12} level is 205 pg per milliliter (151.2 pmol per liter), which is above the lower end of the laboratory reference range. The hematocrit is 42%, with a mean corpuscular volume of 96 fl. The serum methylmalonic acid level is 3600 nmol per liter (normal level, <400), and the serum homocysteine level 49.1 μmol per liter (normal level, <14). How should this patient be further evaluated and treated?

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THE CLINICAL PROBLEM

The recognition and treatment of vitamin B_{12} deficiency is critical since it is a reversible cause of bone marrow failure and demyelinating nervous system disease. Vitamin B_{12} (cobalamin) is synthesized by microorganisms and detected in trace amounts mostly in foods of animal origin.[1] Uptake in the gastrointestinal tract depends on intrinsic factor, which is synthesized by the gastric parietal cells, and on the "cubam receptor" in the distal ileum.[2] The most frequent cause of severe vitamin B_{12} deficiency is a loss of intrinsic factor due to autoimmune atrophic gastritis,[3] historically called "pernicious anemia," even though many patients present with mainly neurologic manifestations.[4,5]

An audio version of this article is available at NEJM.org

PATHOPHYSIOLOGY OF VITAMIN B_{12} DEFICIENCY

Vitamin B_{12} is a cofactor for only two enzymes: methionine synthase and L-methylmalonyl–coenzyme A mutase[6,7] (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The interaction between folate and B_{12} is responsible for the megaloblastic anemia seen in both vitamin deficiencies. Dyssynchrony between the maturation of cytoplasm and that of nuclei leads to macrocytosis, immature nuclei, and hypersegmentation in granulocytes[6] in the peripheral blood (Fig. 1A). The hypercellular and dysplastic bone marrow can be mistaken for signs of acute leukemia (Fig. 1B).[10] The ineffective erythropoiesis results in intramedullary hemolysis and release of lactate dehydrogenase, features that are similar to those of microangiopathic hemolytic anemia.[8] Clinical and laboratory findings of megaloblastic anemia in the peripheral blood and bone marrow are shown in Figure 2.

Vitamin B_{12} is necessary for the development and initial myelination of the central nervous system as well as for the maintenance of its normal function. Demyelination of the cervical and thoracic dorsal and lateral columns of the spinal cord, occasional demyelination of cranial and peripheral nerves, and demyelination of white matter in the brain[5] (i.e., "combined-systems disease" or "subacute combined degeneration") can occur with vitamin B_{12} deficiency (Fig. 2). Pathologi-

KEY CLINICAL POINTS

VITAMIN B_{12} DEFICIENCY

- Vitamin B_{12} deficiency causes reversible megaloblastic anemia, demyelinating neurologic disease, or both.
- Autoimmune gastritis (pernicious anemia) is the most common cause of severe deficiency.
- Methodologic problems may compromise the sensitivity and specificity of current vitamin B_{12} assays.
- Measurement of methylmalonic acid, homocysteine, or both is used to confirm vitamin B_{12} deficiency in untreated patients; an elevated level of methylmalonic acid is more sensitive and specific for the diagnosis.
- For patients with pernicious anemia or malabsorption, lifelong vitamin B_{12} therapy is indicated.
- High-dose oral vitamin B_{12} tablets (1000 to 2000 μg) taken daily are as effective as intramuscular monthly injections in correcting blood and neurologic abnormalities.

cal analysis reveals a "spongy degeneration" due to the loss of and swelling of myelin sheaths; this degeneration is visible on magnetic resonance imaging.[11] For unclear reasons, the severity of megaloblastic anemia is inversely correlated with the degree of neurologic dysfunction.[4,5]

Less common conditions associated with vitamin B_{12} deficiency include glossitis, malabsorption, infertility, and thrombosis (including thrombosis at unusual sites such as cerebral venous sinus thrombosis).[12,13] Thrombosis has been attributed to the marked hyperhomocysteinemia seen in severe cases of vitamin B_{12} deficiency. Patients occasionally have hyperpigmentation, which clears with treatment.[6]

CAUSES OF VITAMIN B_{12} DEFICIENCY

Table 1 and Figure 3 list causes of vitamin B_{12} deficiency and recommended management. Pernicious anemia is discussed below, since this is the most common cause of severe vitamin B_{12} deficiency worldwide.

Dietary vitamin B_{12} deficiency in infants and children is also discussed because of the increasing recognition of severe abnormalities in exclusively breast-fed infants of mothers with vitamin B_{12} deficiency.

Pernicious Anemia

Pernicious anemia[1] is an autoimmune gastritis resulting from the destruction of gastric parietal cells and the associated lack of intrinsic factor to bind ingested vitamin B_{12}. The immune response is directed against the gastric H/K–ATPase, which accounts for associated achlorhydria.[2,3] Other autoimmune disorders, especially thyroid disease, type 1 diabetes mellitus, and vitiligo, are also commonly associated with pernicious anemia. Whether the stomach pathogen *Helicobacter pylori* plays a causative role in pernicious anemia is unclear.[19] Autoimmune gastritis may cause malabsorption of iron, with clinical iron deficiency developing early in life and eventually progressing to malabsorption of vitamin B_{12}.[20] The prevalence of pernicious anemia ranges from 50 to 4000 cases per 100,000 persons, depending on the diagnostic criteria.[1] All age groups are affected, but the median age range in large series is 70 to 80 years.[21,22] Pernicious anemia is more common in persons of African or European ancestry (4.3% and 4.0% prevalence among older adults, respectively) than in those of Asian ancestry.[1,21] Milder forms of atrophic gastritis with hypochlorhydria and an inability to release dietary protein-bound vitamin B_{12} affect up to 20% of older adults.[19,23,24]

Dietary Deficiency in Infancy and Childhood

The infant of a mother with vitamin B_{12} deficiency may be born with the deficiency or it may occur if he or she is exclusively breast-fed,[15,16] usually between 4 and 6 months of age. Typical manifestations of vitamin B_{12} deficiency in children include failure of brain development and overall growth and development, developmental regression, hypotonia, feeding difficulties, lethargy, tremors, hyperirritability, and coma (Fig. 2).[15,16] Brain imaging may reveal atrophy and delayed myelination. Anemia may be present. Vitamin B_{12} replacement results in rapid improvement in responsiveness, and many infants recover fully. However, the longer the period of deficiency, the more likely that there will be permanent disabilities. Mothers of infants with

vitamin B_{12} deficiency often have unrecognized pernicious anemia, but alternatively, they may have a history of gastric bypass surgery, the short-gut syndrome, or a long-term vegetarian or vegan diet.[16] Tandem mass spectrometry, used in neonatal screening programs in all 50 states, may detect nutritional B_{12} deficiency owing to an increase in propionyl carnitine, but direct measurement of methylmalonic acid has higher sensitivity.[25] Other causes of B_{12} deficiency in children, such as ileal resections, the Imerslund–Gräsbeck syndrome, inflammatory bowel disease, and pernicious anemia, are listed in Table 1.[18]

STRATEGIES AND EVIDENCE

EVALUATION

Both the clinical recognition of vitamin B_{12} deficiency and confirmation of the diagnosis by means of testing can be difficult. An approach to testing is shown in Table 2.

The patient's history may include symptoms of anemia, underlying disorders causing malabsorption, and neurologic symptoms. The most common neurologic symptoms are symmetric paresthesias or numbness and gait problems.[4,5] The physical examination may reveal pallor, edema, pigmentary changes in the skin, jaundice, or neurologic defects such as impaired vibration sense, impaired position and cutaneous sensation, ataxia, and weakness (Fig. 2).

Bone marrow biopsy and aspiration are not necessary for the diagnosis of megaloblastic anemia and may be misleading in cases of severe pancytopenia with hypercellularity, increased erythroblasts, and even cytogenetic abnormalities, confusing the diagnosis with acute leukemia.[8-10] Imaging of the spinal cord is not indicated in patients with recognized vitamin B_{12} deficiency, but in cases of severe myelopathy that are not initially recognized as the result of vitamin B_{12} deficiency, there is characteristic hyperintensity on T_2-weighted imaging, described as an inverted V-shaped pattern in the cervical and thoracic spinal cord.[11]

Vitamin B_{12} Assay

The first test performed to confirm the diagnosis of vitamin B_{12} deficiency is generally measurement of the serum vitamin B_{12} level. Although an extremely low level (<100 pg per milliliter [<73.8 pmol per liter]) is usually associated with clinical deficiency, such low levels are infrequently observed. Both false negative and false positive values are common (occurring in up to 50% of tests) with the use of the laboratory-reported lower limit of the normal range as a cutoff point for deficiency.[4,24,26] The high rate of false negative and false positive results may be

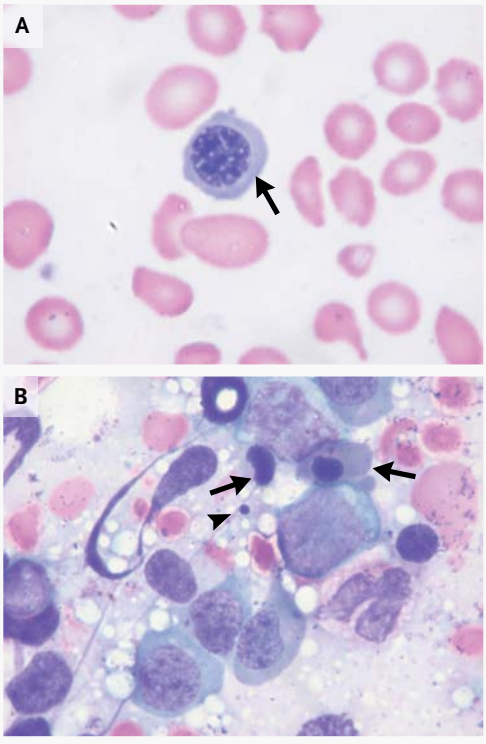

Figure 1. Peripheral-Blood Cells and Bone Marrow Specimen Obtained from a Patient with Vitamin B_{12} Deficiency.

In Panel A, a peripheral-blood smear shows oval macrocytes as well as fragmented, misshapen cells and an immature megaloblastic nucleated red cell (arrow). The variation in red-cell size and shape could lead to a misdiagnosis of microangiopathic hemolytic anemia instead of megaloblastic anemia.[8,9] The mean corpuscular volume was in the normal range, but an extremely high red-cell distribution width suggested macrocytosis combined with microcytic fragmented cells. In Panel B, a bone marrow aspirate shows megaloblastic features. Large erythroblasts and other red-cell precursors are characterized by an open, immature nuclear chromatin pattern. There is dyssynchrony between the maturation of cytoplasm and that of nuclei in later red-cell and granulocyte precursors. A "giant" band is present. Several red-cell precursors have dysplastic nuclei (arrows), with nuclear fragments (arrowhead) that are compatible with cellular apoptosis and resulting intramedullary hemolysis. (Photographs courtesy of John W. Ryder, M.D., Department of Pathology, University of Colorado School of Medicine.)

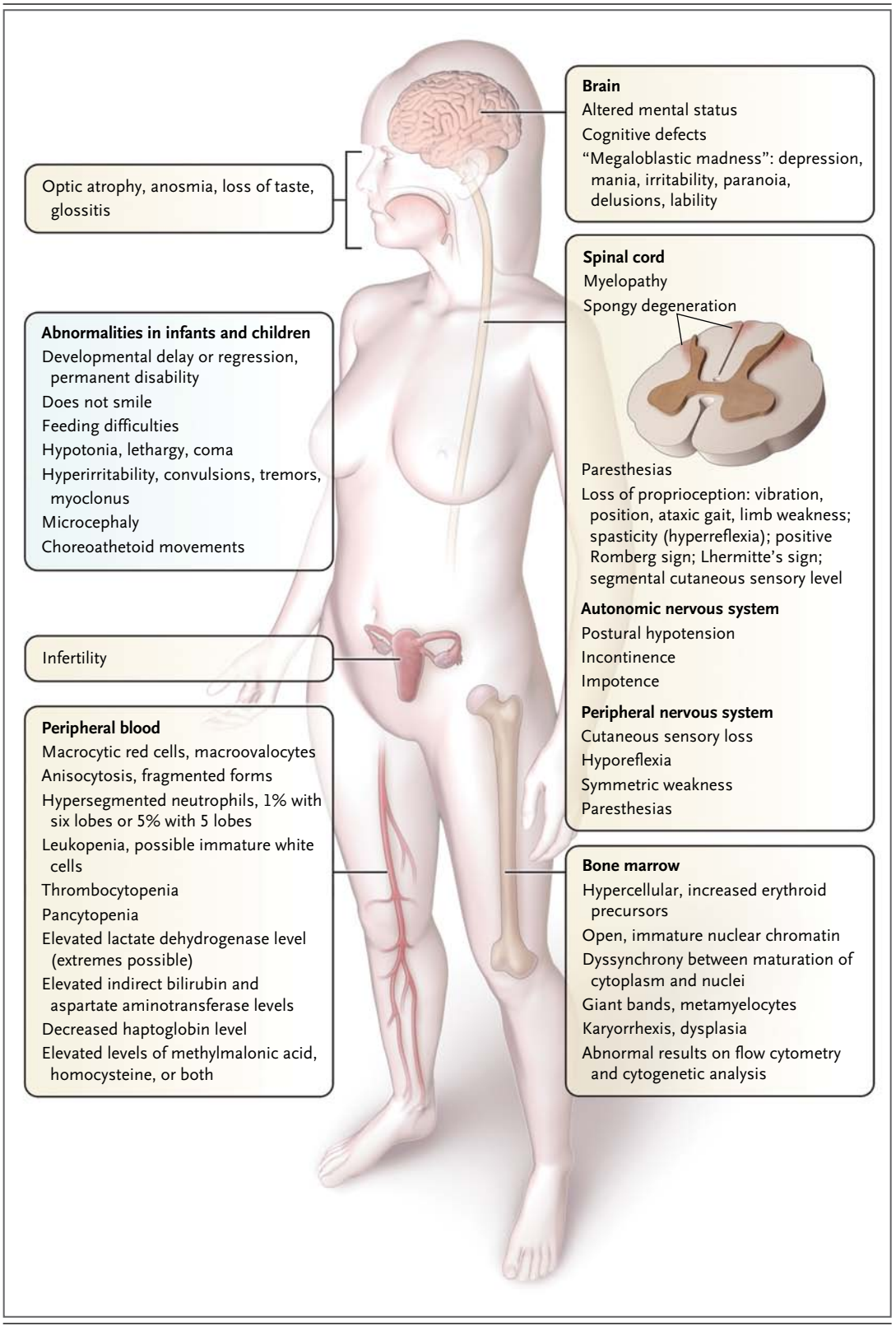

Figure 2 (facing page). Clinical and Laboratory Findings in Vitamin B_{12} Deficiency.

The spectrum of disease associated with vitamin B_{12} deficiency is wide, from asymptomatic to life-threatening pancytopenia or myelopathy. An increase in the mean red-cell volume or distribution width or a mean volume that is higher than expected for the patient's age, presumed iron status (either high or low iron levels), and the presence of thalassemia are important determinants of macrocytosis, rather than an absolute value above the reference range. Cerebral symptoms are usually accompanied by paresthesias and signs of myelopathy or neuropathy.[5]

due to the fact that only 20% of the total measured vitamin B_{12} is on the cellular delivery protein, transcobalamin; the remainder is bound to haptocorrin, a protein of unknown function.[27] Most laboratories now perform automated assays of vitamin B_{12} on platforms used for many other analytes. There is often poor agreement when samples are assayed by different laboratories or with the use of different methods.[31-34] Because intrinsic factor is used as the assay-binding protein, anti–intrinsic factor antibodies (which are common in pernicious anemia) must be removed chemically from the sample, which has proved to be problematic in the automated assays.[33,34] Recent studies show normal values[34] or falsely high values[33] of vitamin B_{12} in many patients with pernicious anemia. New assays of holotranscobalamin (to measure the vitamin B_{12} saturation of transcobalamin) provide a modest improvement in specificity over that provided by assays of total serum vitamin B_{12}, but they have not been clinically validated[27-29] and are not yet available commercially in the United States.

Given the limitations of available assays, clinicians should not use a laboratory's reported lower limit of the normal range to rule out the diagnosis of vitamin B_{12} deficiency in patients with compatible clinical abnormalities. Clinicians should also recognize that vitamin B_{12} values are frequently low in patients without other metabolic or clinical evidence of vitamin B_{12} deficiency (i.e., megaloblastic anemia or myelopathy).

Measurement of Serum Methylmalonic Acid and Total Homocysteine

Measurement of methylmalonic acid, total homocysteine, or both is useful in making the diagnosis of vitamin B_{12} deficiency in patients who have not received treatment.[4,22,24,26,33,35,36] The levels of both methylmalonic acid and total homocysteine are markedly elevated in the vast majority (>98%) of patients with clinical B_{12} deficiency (Fig. 4),[7,22] including those who have only neurologic manifestations of deficiency (i.e., no anemia).[4,22]

Elevated levels of methylmalonic acid and total homocysteine decrease immediately after treatment, and the levels can be remeasured to document adequate vitamin B_{12} replacement. Levels of these metabolites are normal in up to 50% of patients with low vitamin B_{12} levels who have no hematologic or neurologic response to replacement therapy, indicating that the low values are false positive results.[26] Given the limitations of vitamin B_{12} assays in confirming the diagnosis of B_{12} deficiency,[31,34] it may be prudent to measure methylmalonic acid, total homocysteine, or both in patients with compatible clinical findings or provide empirical treatment with the use of defined end points to document a clinical response.

An elevated level of methylmalonic acid is reasonably specific for vitamin B_{12} deficiency, and the level always decreases with vitamin B_{12} therapy.[24,36] Modest increases (to 300 to 700 nmol per liter) occur with renal failure.[36,37] However, nearly all patients with megaloblastic anemia or myelopathy have levels of methylmalonic acid that are higher than 500 nmol per liter, and 86% have levels that are higher than 1000 nmol per liter (Fig. 3). The level of serum total homocysteine is less specific, since it is also elevated in folate deficiency,[22,35] classic homocystinuria, and renal failure.

TESTS TO DETERMINE THE CAUSE OF VITAMIN B_{12} DEFICIENCY

If the patient consumes sufficient amounts of vitamin B_{12} and has clinically confirmed B_{12} deficiency, then malabsorption must be present. Testing for pernicious anemia is described in Table 2. A positive test for anti–intrinsic factor or anti–parietal-cell antibodies is indicative of pernicious anemia; surveillance for autoimmune thyroid disease is reasonable in patients with positive antibody tests. Chronic atrophic gastritis can be diagnosed on the basis of an elevated fasting serum gastrin level and a low level of serum pepsinogen I.[3,19] Some experts recommend endoscopy to confirm gastritis and rule out gastric carcinoid and other gastric cancers, since patients with pernicious anemia are at increased risk for such cancers.[3]

The Schilling test of radioactive vitamin B_{12}

Table 1. Causes and Treatment of Vitamin B_{12} Deficiency.

Cause	Treatment	Follow-up
Severe malabsorption		
Pernicious anemia (autoimmune gastritis)	Intramuscular cyanocobalamin at a dose of 1000 μg administered intramuscularly daily or every other day for 1 wk, then weekly for 4 to 8 wk, and then monthly for life, or oral cyanocobalamin at a daily dose of 1000 to 2000 μg for life*	Administer iron and folate replacement as needed for full hemoglobin response, especially in patients with intestinal disease; perform surveillance for other autoimmune conditions, especially thyroid disease in patients with pernicious anemia; perform upper endoscopy in patients with symptoms of gastric cancer† or iron deficiency
Total or partial gastrectomy	Same as for pernicious anemia	Same as for pernicious anemia
Gastric bypass or other bariatric surgery	Same as for pernicious anemia	Same as for pernicious anemia
Ileal resection or organ reconstructive surgery (ileal conduit diversion and ileocystoplasty)	Same as for pernicious anemia	Same as for pernicious anemia
Inflammatory bowel disease, tropical sprue	Same as for pernicious anemia	Same as for pernicious anemia
Imerslund–Gräsbeck and other syndromes‡	Same as for pernicious anemia	Genetic counseling to detect vitamin B_{12} deficiency in family members
Mild malabsorption		
Protein-bound vitamin B_{12} malabsorption	Oral cyanocobalamin at a dose of 500 to 1000 μg daily or intramuscular cyanocobalamin at a dose of 1000 μg daily or every other day for 1 wk, then weekly for 4 to 8 wk, and then monthly for life	Perform tests for iron deficiency, anemia of chronic kidney disease, and anemia of chronic inflammation; these conditions coexist frequently in older adults, may limit the response to treatment, and may require further treatment
Mild atrophic gastritis	Same as for protein-bound vitamin B_{12} malabsorption	Same as for protein-bound vitamin B_{12} malabsorption
Use of metformin[14]	Same as for protein-bound vitamin B_{12} malabsorption	Same as for protein-bound vitamin B_{12} malabsorption
Use of drugs that block stomach acid	Same as for protein-bound vitamin B_{12} malabsorption	Same as for protein-bound vitamin B_{12} malabsorption
Dietary deficiency		
Adults		
Vegan or vegetarian diet, or diet low in meat and dairy products	Supplements containing >2 μg of vitamin B_{12} or foods fortified with vitamin B_{12}	Perform tests for iron deficiency, which is very common
Infants		
Breast-feeding in infants with vitamin B_{12}–deficient mothers[15,16]	Intramuscular cyanocobalamin at a dose of 250 to 1000 μg daily, then weekly until patient recovers; treatment of mother to enrich breast milk; oral supplementation with 1 to 2 μg of vitamin B_{12} daily or vitamin B_{12}–enriched formula or food	Confirm metabolic response in infants or refer parents to genetics specialist for evaluation; provide nutritional counseling for mothers

Children		
Diseases similar to those causing malabsorption in adults	100 μg of intramuscular vitamin B_{12} monthly or high-dose oral vitamin B_{12} daily in younger children; treatment as per adults in older children	Confirm pernicious anemia or congenital malabsorption
Recreational or occupational abuse of nitrous oxide§	Intramuscular cyanocobalamin at a dose of 1000 μg administered on the same schedule as that for pernicious anemia above and for life if underlying pernicious anemia is present	Evaluate for vitamin B_{12} malabsorption; provide addiction counseling
Nitrous oxide anesthesia in occult pernicious anemia[17]		

* Intramuscular hydroxocobalamin can be substituted for intramuscular cyanocobalamin, but document the long-term response if it is administered at 3-month intervals.
† Experts are not in agreement about the necessity or frequency of routine upper endoscopy in patients with pernicious anemia. However, symptoms suggestive of gastric carcinoma, unexplained iron deficiency, and proven gastrointestinal blood loss should prompt a full investigation.
‡ Congenital malabsorption of vitamin B_{12} results from mutations of the ileal cubam receptor, cubilin, or amnionless (as in the Imerslund–Gräsbeck syndrome) and from mutations in gastric intrinsic factor. These syndromes are usually manifested in infancy and early childhood, although studies have shown a delay in onset even into adolescence.[18]
§ Nitrous oxide inactivates the vitamin B_{12}–dependent enzyme methionine synthase and causes formation of vitamin B_{12} analogues and gradual tissue depletion of vitamin B_{12}.

absorption is no longer available. A potential replacement absorption test is under development wherein the increase in vitamin B_{12} saturation of holotranscobalamin is measured after several days of oral B_{12} loading,[39] but this requires further study.

TREATMENT OF VITAMIN B_{12} DEFICIENCY

The daily requirement of vitamin B_{12} has been set at 2.4 μg,[40,41] but higher amounts — 4 to 7 μg per day — which are common in persons who eat meat or take a daily multivitamin, are associated with lower methylmalonic acid values.[42] Healthy older adults should consider taking supplemental crystalline vitamin B_{12} as recommended by the Food and Nutrition Board.[41] However, most patients with clinical vitamin B_{12} deficiency have malabsorption and will require parenteral or high-dose oral replacement. Adequate supplementation results in resolution of megaloblastic anemia and resolution of or improvement in myelopathy.

Injected Vitamin B_{12}

There are many recommended schedules for injections of vitamin B_{12} (called cyanocobalamin in the United States and hydroxocobalamin in Europe).[6,23] About 10% of the injected dose (100 of 1000 μg) is retained. Patients with severe abnormalities should receive injections of 1000 μg at least several times per week for 1 to 2 weeks, then weekly until clear improvement is shown, followed by monthly injections. Hematologic response is rapid, with an increase in the reticulocyte count in 1 week and correction of megaloblastic anemia in 6 to 8 weeks. Patients with severe anemia and cardiac symptoms should be treated with transfusion and diuretic agents, and electrolytes should be monitored. Neurologic symptoms may worsen transiently and then subside over weeks to months.[5] The severity and duration of the neurologic abnormalities before treatment influence the eventual degree of recovery.[4,5] Treatment of pernicious anemia is lifelong. In patients in whom vitamin B_{12} supplementation is discontinued after clinical recovery, neurologic symptoms recur within as short a period as 6 months, and megaloblastic anemia recurs in several years.[6]

High-Dose Oral Treatment

High-dose oral treatment is effective and is increasingly popular. A study performed 45 years ago

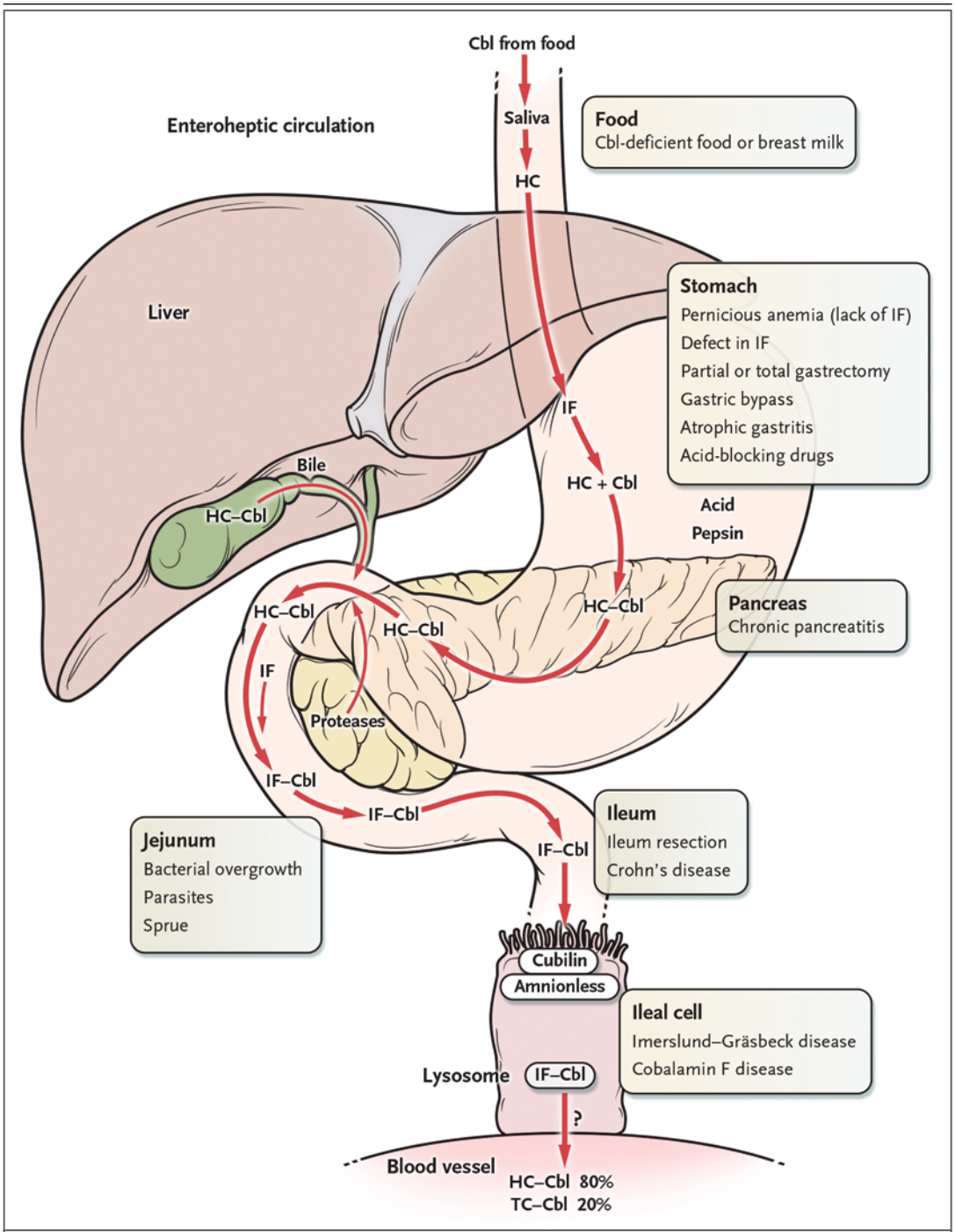

Figure 3. The Normal Mechanisms and Defects of Absorption of Vitamin B_{12}.

The vitamin B_{12} (Cbl) released from food protein by peptic action is bound to haptocorrin (HC) in the stomach and travels to the duodenum, where pancreatic proteases digest the HC, releasing Cbl to bind to intrinsic factor (IF). The IF-Cbl complex binds to a specific receptor in the distal ileum (the cubam receptor) and is internalized, eventually released from lysosomes, and transported into the blood. Both HC and transcobalamin (TC) bind Cbl in the circulation, although the latter is the cellular delivery protein. Adapted from Stabler.[6]

Table 2. Laboratory Testing in Vitamin B_{12} Deficiency.*

Test	Sensitivity	Specificity	Comments
Measurement to detect deficiency			
Serum vitamin B_{12} <200 pg/ml or laboratory cutoff level	65–95% for proven clinical deficiency†; 50% for detecting elevated level of methylmalonic acid	50–60% for clinical response†; 80% for detecting elevated level of methylmalonic acid	Current vitamin B_{12} assays are especially problematic in patients with anti–intrinsic factor antibodies
Serum vitamin B_{12} <350 pg/ml	90%	25% for detecting elevated level of methylmalonic acid	
Holotranscobalamin <20 to 45 pmol/liter‡	Insufficient data on sensitivity for clinical deficiency; 46–89% for detecting elevated level of methylmalonic acid	Insufficient data on specificity for clinical deficiency; 28–96% for detecting elevated level of methylmalonic acid	Levels of holotranscobalamin increase in renal failure; superior to measurement of total vitamin B_{12} in pregnancy, when the total level decreases
Serum methylmalonic acid >400 nmol/liter§	98% for clinical deficiency	Poor specificity for clinical response in patients with modest elevation of level of methylmalonic acid (300–1000 nmol/liter)¶	Renal failure and volume depletion may increase level of serum methylmalonic acid, but rarely to >1000 nmol/liter
Serum or plasma total homocysteine >21 μmol/liter	96% for clinical deficiency	Homocysteine level also increased in clinical folate deficiency and renal insufficiency	
Test to determine cause of deficiency‖			
Pernicious anemia			
Anti–intrinsic factor antibodies	50%	100%	Must be tested >7 days after vitamin B_{12} injection to prevent false positive result
Anti–parietal-cell antibodies	80%	50–100%	
Atrophic body gastritis (antral sparing)**			
Fasting high serum gastrin level (>100 pmol/liter)	85%		
Low level of serum pepsinogen I (<30 μg/liter)	90%		
Endoscopy with pentagastrin-fast hypochlorhydria		100%	Rarely performed
Malabsorption of vitamin B_{12}††			
Vitamin B_{12} absorption test			Schilling test no longer available
Increase in serum holotranscobalamin level after oral loading	Unknown	Unknown	Promising preclinical data, but still experimental

* To convert the values for vitamin B_{12} to picomoles per liter, multiply by 0.7378.
† Available assays are largely chemiluminescent microparticle immunoassays performed with the use of automated analyzers that in general show higher values than the radiodilution and microbiologic assays used in past studies of clinically confirmed deficiency.[4,22,24,26] Thus, these tests are likely to have lower sensitivities and specificities than the older assays.
‡ The holotranscobalamin assay has been studied widely in Europe[27-30] but is not yet commercially available in the United States. The appropriate lower end of the reference range is still under debate.[33] The values for sensitivity and specificity are reviewed in Heil et al.[29]
§ Urinary methylmalonic acid has not been extensively studied, but values greater than 2.5 μmol per millimole of creatinine suggest deficiency.
¶ Elevated levels of methylmalonic acid fall with vitamin B_{12} therapy, but an associated clinical response is highly variable, depending largely on the presence of vitamin B_{12}–related disease.
‖ Evidence of a causal pathologic process does not confirm coexisting B_{12} deficiency, since underlying gastrointestinal disease may predate the deficiency by many years.
** The relationship between atrophic body gastritis (autoimmune gastritis) and infection with *Helicobacter pylori* is variable. Antral sparing is a type of atrophic body gastritis in which the cells in the antrum can produce high levels of gastrin.
†† There is malabsorption if clinically proven vitamin B_{12} deficiency is present in a patient who eats meat, receives multivitamin therapy, or both.

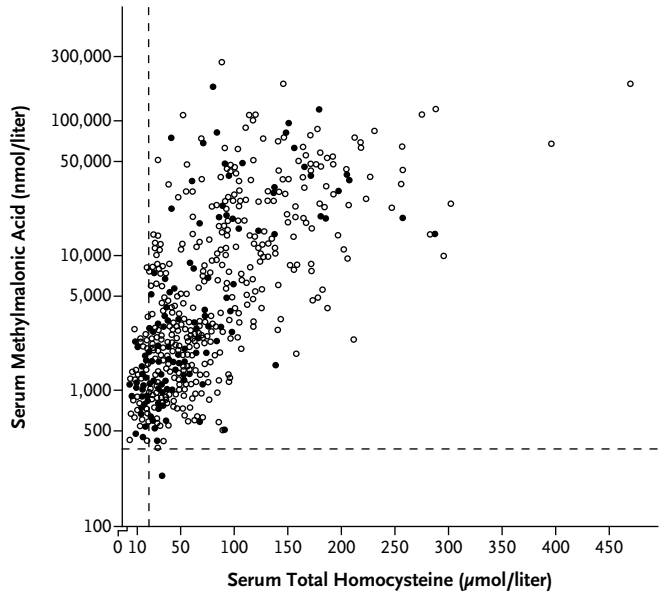

Figure 4. Serum Methylmalonic Acid and Total Homocysteine Concentrations in 491 Episodes of Vitamin B_{12} Deficiency.

The data shown have been combined from studies performed over a period of 25 years.[4,6,22,24,26,35,37,38] Most of the patients with clinically confirmed vitamin B_{12} deficiency had documented pernicious anemia and a proven response to vitamin B_{12} therapy. Open circles indicate episodes in patients with a hematocrit lower than 38%, and solid circles indicate episodes in those with a hematocrit of 38% or higher. Patients without anemia had neurologic manifestations of vitamin B_{12} deficiency and similar values of methylmalonic acid and total homocysteine. The axis for serum methylmalonic acid is plotted on a log scale. The dashed lines indicate values that are 3 SD above the mean for healthy blood donors: 376 nmol per liter for methylmalonic acid and 21.3 μmol per liter for total homocysteine. The level of methylmalonic acid was greater than 500 nmol per liter in 98% of the patients and greater than 1000 nmol per liter in 86%. Adapted from Stabler.[7]

showed that 0.5 to 4% of radioactively labeled oral vitamin B_{12} can be absorbed by passive diffusion in both normal controls and patients with pernicious anemia.[43] Thus, oral doses of 1000 μg deliver 5 to 40 μg, even if taken with food.

A randomized trial that compared an oral dose of 2000 μg daily with parenteral therapy (seven injections of 1000 μg of cyanocobalamin over a period of 1 month, followed by monthly injections) in patients with pernicious anemia, atrophic gastritis, or a history of ileal resection showed similar reductions in the mean corpuscular volume and increases in the hematocrit at 4 months in both groups.[38] All participants (four in each group) with paresthesias, ataxia, or memory loss had resolution or improved with treatment. However, levels of methylmalonic acid after treatment were significantly lower with daily oral treatment (169 nmol per liter, vs. 265 nmol per liter with parenteral treatment) and vitamin B_{12} levels were significantly higher (1005 pg per milliliter vs. 325 pg per milliliter [741.5 vs. 239.8 pmol per liter]). A more recent trial with a similar design involving a proprietary oral vitamin B_{12} preparation also revealed significantly lower levels of methylmalonic acid in the oral-treatment group at the 3-month follow-up.[30] In a randomized trial comparing oral with intramuscular vitamin B_{12} (1000-μg doses, daily for 10 days, then weekly for 4 weeks, and monthly thereafter), the two groups had similar improvements in hematologic abnormalities and vitamin B_{12} levels at 90 days.[44] Case series of patients treated with oral vitamin B_{12} have yielded variable results; elevated levels of methylmalonic acid, homocysteine, or both were reported in about half of patients with malabsorption who were treated with twice-weekly oral doses of 1000 μg,[45] whereas normal homocysteine levels were reported in patients treated with 1500 μg daily after gastrectomy.[46] Data are lacking from long-term studies to assess whether oral treatment is effective when doses are administered less frequently than daily. Studies involving older adults, many of whom had chronic atrophic gastritis, showed that 60% required large oral doses (>500 μg daily) to correct elevated levels of methylmalonic acid.[47,48]

Proponents of parenteral therapy state that compliance and monitoring are better in patients who receive this form of therapy because they have frequent contact with health care providers, whereas proponents of oral therapy maintain that compliance will be improved in patients who receive oral therapy because of convenience, comfort, and decreased expense. High-dose vitamin B_{12} tablets (500 to 1500 μg) are available in the United States without a prescription. Self-administered injections are also easily taught, economical, and in my experience, effective. Patients should be informed of the pros and cons of oral versus parenteral therapy, and regardless of the form of treatment, those with pernicious anemia or malabsorption should be reminded of the need for lifelong replacement.

AREAS OF UNCERTAINTY

Vitamin B_{12} deficiency is the major cause of hyperhomocysteinemia in countries with folate-fortified food, such as the United States and

Canada. Epidemiologic studies show significant associations between elevated homocysteine levels and vascular disease and thrombosis. However, large randomized trials of combined high-dose vitamin B therapy in patients with vascular disease have shown no reduction in vascular events.[49] Vitamin B_{12} status should be evaluated in patients with hyperhomocysteinemia before folic acid treatment is initiated.

The potential role of mild vitamin B_{12} deficiency in cognitive decline with aging remains uncertain. Epidemiologic studies indicate an inverse association between vitamin B_{12} supplementation and neurodegenerative disease, but results of randomized trials have been largely negative.[50]

Besides oral tablets, vitamin B is available in sublingual preparations, oral sprays, nasal gels or sprays, and transdermal patches. Data on the absorption and efficacy of these alternative preparations are lacking.

GUIDELINES

Nutritional guidelines for vitamin B_{12} intake are published by the Food and Nutrition Board,[41] and nutritional guidelines for vegetarians are published by the American Dietetic Association.[40] There are no recommendations from the American Society of Hematology for the diagnosis and treatment of vitamin B_{12} deficiency. The American Academy of Neurology recommends measurements of vitamin B_{12}, methylmalonic acid, and homocysteine in patients with symmetric polyneuropathy.[51] The American Society for Gastrointestinal Endoscopy recommends a single endoscopic evaluation at the diagnosis of pernicious anemia.[52]

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has neurologic abnormalities that are consistent with vitamin B_{12} deficiency. Since vitamin B_{12} levels may be above the lower end of the laboratory reference range even in patients with clinical deficiency, methylmalonic acid, total homocysteine, or both should be measured to document vitamin B_{12} deficiency before treatment is initiated; the elevated levels in this patient confirm the diagnosis. In the absence of dietary restriction or a known cause of malabsorption, further evaluation is warranted — in particular, testing for pernicious anemia (anti–intrinsic factor antibodies). Either parenteral vitamin B_{12} treatment (8 to 10 loading injections of 1000 μg each, followed by monthly 1000-μg injections), or high-dose oral vitamin B_{12} treatment (1000 to 2000 μg daily) is an effective therapy. I would review both options (including the possibility of self-injection at home) with the patient. Effective vitamin replacement will correct blood counts in 2 months and correct or improve neurologic signs and symptoms within 6 months.

Dr. Stabler reports holding patents (assigned to the University of Colorado and Competitive Technologies) on the use of homocysteine, methylmalonic acid, and other metabolites in the diagnosis of vitamin B_{12} and folate deficiency, but no longer receiving royalties for these patents. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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