Vitamin B<sub>12</sub> Deficiency
Sally P. Stabler, M.D.

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<sub>12</sub> level is 205 pg per milliliter (151.2 pmol per liter), which is above the lower end of the laboratory reference range. The hemato-crit 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?

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.

**THE CLINICAL PROBLEM**

The recognition and treatment of vitamin B<sub>12</sub> deficiency is critical since it is a reversible cause of bone marrow failure and demyelinating nervous system disease. Vitamin B<sub>12</sub> (cobalamin) is synthesized by microorganisms and detected in trace amounts mostly in foods of animal origin. 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. The most frequent cause of severe vitamin B<sub>12</sub> deficiency is a loss of intrinsic factor due to autoimmune atrophic gastritis, historically called “pernicious anemia,” even though many patients present with mainly neurologic manifestations.

**PATHOPHYSIOLOGY OF VITAMIN B<sub>12</sub> DEFICIENCY**

Vitamin B<sub>12</sub> is a cofactor for only two enzymes: methionine synthase and l-methylmalonyl–coenzyme A mutase (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The interaction between folate and B<sub>12</sub> 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 in the peripheral blood (Fig. 1A). The hypercellular and dysplastic bone marrow can be mistaken for signs of acute leukemia (Fig. 1B). The ineffective erythropoiesis results in intramedullary hemolysis and release of lactate dehydrogenase, features that are similar to those of microangiopathic hemolytic anemia. Clinical and laboratory findings of megaloblastic anemia in the peripheral blood and bone marrow are shown in Figure 2.

Vitamin B<sub>12</sub> 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 (i.e., “combined-systems disease” or “subacute combined degeneration”) can occur with vitamin B<sub>12</sub> deficiency (Fig. 2). Patholog-
VITAMIN B₁₂ DEFICIENCY

- Vitamin B₁₂ 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 B₁₂ assays.
- Measurement of methylmalonic acid, homocysteine, or both is used to confirm vitamin B₁₂ 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 B₁₂ therapy is indicated.
- High-dose oral vitamin B₁₂ tablets (1000 to 2000 µg) taken daily are as effective as intramuscular monthly injections in correcting blood and neurologic abnormalities.

CAUSES OF VITAMIN B₁₂ DEFICIENCY

Table 1 and Figure 3 list causes of vitamin B₁₂ deficiency and recommended management. Pernicious anemia is discussed below, since this is the most common cause of severe vitamin B₁₂ deficiency worldwide.

Dietary vitamin B₁₂ 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 B₁₂ deficiency.

Pernicious Anemia

Pernicious anemia is an autoimmune gastritis resulting from the destruction of gastric parietal cells and the associated lack of intrinsic factor to bind ingested vitamin B₁₂. The immune response is directed against the gastric H/K-ATPase, which accounts for associated achlorhydria. 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. Autoimmune gastritis may cause malabsorption of iron, with clinical iron deficiency developing early in life and eventually progressing to malabsorption of vitamin B₁₂. The prevalence of pernicious anemia ranges from 50 to 4000 cases per 100,000 persons, depending on the diagnostic criteria. All age groups are affected, but the median age range in large series is 70 to 80 years. 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. Milder forms of atrophic gastritis with hypochlorhydria and an inability to release dietary protein-bound vitamin B₁₂ affect up to 20% of older adults.

Dietary Deficiency in Infancy and Childhood

The infant of a mother with vitamin B₁₂ deficiency may be born with the deficiency or it may occur if he or she is exclusively breast-fed, usually between 4 and 6 months of age. Typical manifestations of vitamin B₁₂ deficiency in children include failure of brain development and overall growth and development, developmental regression, hypotonia, feeding difficulties, lethargy, tremors, hyperirritability, and coma. Brain imaging may reveal atrophy and delayed myelination. Anemia may be present. Vitamin B₁₂ 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 B₁₂ 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. Tandem mass spectrometry, used in neonatal screening programs in all 50 states, may detect nutritional B₁₂ deficiency owing to an increase in propionyl carnitine, but direct measurement of methylmalonic acid has higher sensitivity. Other causes of B₁₂ deficiency in children, such as ileal resections, the Imerslund–Gräsbeck syndrome, inflammatory bowel disease, and pernicious anemia, are listed in Table 1.

**STRATEGIES AND EVIDENCE**

**EVALUATION**

Both the clinical recognition of vitamin B₁₂ 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. 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. Imaging of the spinal cord is not indicated in patients with recognized vitamin B₁₂ deficiency, but in cases of severe myelopathy that are not initially recognized as the result of vitamin B₁₂ deficiency, there is characteristic hyperintensity on T₂-weighted imaging, described as an inverted V-shaped pattern in the cervical and thoracic spinal cord.

**Vitamin B₁₂ Assay**

The first test performed to confirm the diagnosis of vitamin B₁₂ deficiency is generally measurement of the serum vitamin B₁₂ 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. The high rate of false negative and false positive results may be
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Brain
- Altered mental status
- Cognitive defects
- "Megaloblastic madness": depression, mania, irritability, paranoia, delusions, lability

Optic atrophy, anosmia, loss of taste, glossitis

Abnormalities in infants and children
- Developmental delay or regression, permanent disability
- Does not smile
- Feeding difficulties
- Hypotonia, lethargy, coma
- Hyperirritability, convulsions, tremors, myoclonus
- Microcephaly
- Choreoathetoid movements

Infertility

Peripheral blood
- Macrocytic red cells, macroovalocytes
- Anisocytosis, fragmented forms
- Hypersegmented neutrophils, 1% with six lobes or 5% with 5 lobes
- Leukopenia, possible immature white cells
- Thrombocytopenia
- Pancytopenia
- Elevated lactate dehydrogenase level (extremes possible)
- Elevated indirect bilirubin and aspartate aminotransferase levels
- Decreased haptoglobin level
- Elevated levels of methylmalonic acid, homocysteine, or both

Bone marrow
- Hypercellular, increased erythroid precursors
- Open, immature nuclear chromatin
- Dysynchrony between maturation of cytoplasm and nuclei
- Giant bands, metamyelocytes
- Karyorrhexis, dysplasia
- Abnormal results on flow cytometry and cytogenetic analysis

Spinal cord
- Myelopathy
- Spongy degeneration
- Paresthesias
- Loss of proprioception: vibration, position, ataxic gait, limb weakness; spasticity (hyperreflexia); positive Romberg sign; Lhermitte’s sign; segmental cutaneous sensory level

Autonomic nervous system
- Postural hypotension
- Incontinence
- Impotence

Peripheral nervous system
- Cutaneous sensory loss
- Hyporeflexia
- Symmetric weakness
- Paresthesias

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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. 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. 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. Recent studies show normal values or falsely high values of vitamin B$_{12}$ in many patients with pernicious anemia. New assays of holo transcobalamin (to measure the vitamin B$_{12}$ saturation of transcobalamin) provide a modest improvement in specificity over that provided by assays of total haptocorrin, a protein of unknown function. Because of intrinsic factor, then malabsorption must be present. 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. The levels of both methylmalonic acid and total homocysteine are markedly elevated in the vast majority (>98%) of patients with clinical vitamin B$_{12}$ deficiency (Fig. 4), including those who have only neurologic manifestations of deficiency (i.e., no anemia).

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. Given the limitations of vitamin B$_{12}$ assays in confirming the diagnosis of vitamin B$_{12}$ deficiency, 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. Modest increases (to 300 to 700 nmol per liter) occur with renal failure. 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, 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. 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.

The Schilling test of radioactive vitamin B$_{12}$...
### Table 1. Causes and Treatment of Vitamin B<sub>12</sub> Deficiency.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe malabsorption (autoimmune gastritis)</td>
<td>Intermuscular 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.</td>
<td>Same as for pernicious anemia</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>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.</td>
<td>Same as for pernicious anemia</td>
</tr>
<tr>
<td>Total or partial gastrectomy</td>
<td>Same as for pernicious anemia</td>
<td>Same as for pernicious anemia</td>
</tr>
<tr>
<td>Gastric bypass or other bariatric surgery</td>
<td>Same as for pernicious anemia</td>
<td>Same as for pernicious anemia</td>
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<tr>
<td>Inflammatory bowel disease, tropical sprue</td>
<td>Same as for pernicious anemia</td>
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</tr>
<tr>
<td>Dietary deficiency</td>
<td>Adult: Supplements containing &gt;2 µg of vitamin B&lt;sub&gt;12&lt;/sub&gt; or foods fortified.</td>
<td>Perform tests for iron deficiency, which is very common</td>
</tr>
<tr>
<td>Infants</td>
<td>Breastfeeding in infants with vitamin B&lt;sub&gt;12&lt;/sub&gt;-deficient mothers.</td>
<td>Confirm metabolic response in infants or refer parents to genetic counseling specialist for evaluation, provide nutritional counseling.</td>
</tr>
</tbody>
</table>

**Notes:**
- Same as for pernicious anemia
- Genetic counseling to detect vitamin B<sub>12</sub> deficiency in family members
- Administer iron and folate replacement as needed for full hemoglobin response, especially for patients with iron deficiency
- Administer vitamin B<sub>12</sub> for other autoimmune diseases, especially for patients with pernicious anemia, especially for patients with symptoms of vitamin B<sub>12</sub> deficiency
- Perform surveillance for other autoimmune conditions, perform upper endoscopy in patients with symptoms of gastric cancer
- Administer vitamin B<sub>12</sub> to detect vitamin B<sub>12</sub> deficiency in family members
**Clinical Practice**

| Children |
|-----------------|-----------------|-----------------|
| Diseases similar to those causing malabsorption in adults | 100 μg of intramuscular vitamin B₁₂, monthly or high-dose oral vitamin B₁₂ 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 B₁₂ malabsorption; provide addiction counseling |

Nitrous oxide anesthesia in occult pernicious anemia

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* 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 B₁₂ results from mutations of the ileal cubam receptor, cublin, 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.
§ Nitrous oxide inactivates the vitamin B₁₂-dependent enzyme methionine synthase and causes formation of vitamin B₁₂ analogues and gradual tissue depletion of vitamin B₁₂.

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Figure 3. The Normal Mechanisms and Defects of Absorption of Vitamin B₁₂.

The vitamin B₁₂ (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>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td><strong>Measurement to detect deficiency</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Serum vitamin B₁₂ &lt;200 pg/ml or laboratory cutoff level</td>
<td>65–95% for proven clinical deficiency; 50% for detecting elevated level of methylmalonic acid</td>
<td>50–60% for clinical response; 80% for detecting elevated level of methylmalonic acid</td>
<td>Current vitamin B₁₂ assays are especially problematic in patients with anti–intrinsic factor antibodies</td>
</tr>
<tr>
<td>Serum vitamin B₁₂ &lt;350 pg/ml</td>
<td></td>
<td>90%</td>
<td></td>
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<tr>
<td>Holotranscobalamin &lt;20 to 45 pmol/liter‡</td>
<td>Insufficient data on sensitivity for clinical deficiency; 46–89% for detecting elevated level of methylmalonic acid</td>
<td>Insufficient data on specificity for clinical deficiency; 28–96% for detecting elevated level of methylmalonic acid</td>
<td>Levels of holotranscobalamin increase in renal failure; superior to measurement of total vitamin B₁₂ in pregnancy, when the total level decreases</td>
</tr>
<tr>
<td>Serum methylmalonic acid &gt;400 nmol/liter§</td>
<td>98% for clinical deficiency</td>
<td>Poor specificity for clinical response in patients with modest elevation of level of methylmalonic acid (300–1000 nmol/liter)¶</td>
<td>Renal failure and volume depletion may increase level of serum methylmalonic acid, but rarely to &gt;1000 nmol/liter</td>
</tr>
<tr>
<td>Serum or plasma total homocysteine &gt;21 µmol/liter</td>
<td>96% for clinical deficiency</td>
<td>Homocysteine level also increased in clinical folate deficiency and renal insufficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Test to determine cause of deficiency‖</strong></td>
<td></td>
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<tr>
<td>Pernicious anemia</td>
<td></td>
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<tr>
<td>Anti–intrinsic factor antibodies</td>
<td>50%</td>
<td>100%</td>
<td>Must be tested &gt;7 days after vitamin B₁₂ injection to prevent false positive result</td>
</tr>
<tr>
<td>Anti–parietal-cell antibodies</td>
<td>80%</td>
<td>50–100%</td>
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<tr>
<td>Atrophic body gastritis (antral sparing)**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting high serum gastrin level (&gt;100 pmol/liter)</td>
<td>85%</td>
<td></td>
<td></td>
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<tr>
<td>Low level of serum pepsinogen I (&lt;30 µg/liter)</td>
<td>90%</td>
<td></td>
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<tr>
<td>Endoscopy with pentagastrin-fast hypochlorhydra</td>
<td></td>
<td>100%</td>
<td>Rarely performed</td>
</tr>
<tr>
<td>Malabsorption of vitamin B₁₂††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂ absorption test</td>
<td></td>
<td></td>
<td>Schilling test no longer available</td>
</tr>
<tr>
<td>Increase in serum holotranscobalamin level after oral loading</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Promising preclinical data, but still experimental</td>
</tr>
</tbody>
</table>

* To convert the values for vitamin B₁₂ 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. Thus, these tests are likely to have lower sensitivities and specificities than the older assays.
‡ The holotranscobalamin assay has been studied widely in Europe but is not yet commercially available in the United States. The appropriate lower end of the reference range is still under debate. 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 B₁₂ therapy, but an associated clinical response is highly variable, depending largely on the presence of vitamin B₁₂–related disease.
‖ Evidence of a causal pathologic process does not confirm coexisting B₁₂ 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 B₁₂ 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. 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.

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. 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, whereas normal homocysteine levels were reported in patients treated with 1500 μg daily after gastrectomy. 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.

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. Vitamin $\text{B}_{12}$ status should be evaluated in patients with hyperhomocysteinemia before folic acid treatment is initiated.

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

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

**Conclusions and Recommendations**

The patient in the vignette has neurologic abnormalities that are consistent with vitamin $\text{B}_{12}$ deficiency. Since vitamin $\text{B}_{12}$ 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 $\text{B}_{12}$ 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 $\text{B}_{12}$ treatment (8 to 10 loading injections of 1000 μg each, followed by monthly 1000-μg injections), or high-dose oral vitamin $\text{B}_{12}$ 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 $\text{B}_{12}$ 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.

**References**

15. Dror DK, Allen LH. Effect of vitamin


