

# Vitamin B<sub>12</sub> Deficiency

ROBERT C. OH, CPT, MC, USA, U.S. Army Health Clinic, Darmstadt, Germany  
DAVID L. BROWN, MAJ, MC, USA, Madigan Army Medical Center, Fort Lewis, Washington

Vitamin B<sub>12</sub> (cobalamin) deficiency is a common cause of macrocytic anemia and has been implicated in a spectrum of neuropsychiatric disorders. The role of B<sub>12</sub> deficiency in hyperhomocysteinemia and the promotion of atherosclerosis is only now being explored. Diagnosis of vitamin B<sub>12</sub> deficiency is typically based on measurement of serum vitamin B<sub>12</sub> levels; however, about 50 percent of patients with subclinical disease have normal B<sub>12</sub> levels. A more sensitive method of screening for vitamin B<sub>12</sub> deficiency is measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B<sub>12</sub> deficiency. Use of the Schilling test for detection of pernicious anemia has been supplanted for the most part by serologic testing for parietal cell and intrinsic factor antibodies. Contrary to prevailing medical practice, studies show that supplementation with oral vitamin B<sub>12</sub> is a safe and effective treatment for the B<sub>12</sub> deficiency state. Even when intrinsic factor is not present to aid in the absorption of vitamin B<sub>12</sub> (pernicious anemia) or in other diseases that affect the usual absorption sites in the terminal ileum, oral therapy remains effective. (*Am Fam Physician* 2003;67:979-86,993-4. Copyright© 2003 American Academy of Family Physicians.)

● A patient information handout on vitamin B<sub>12</sub> deficiency, written by the authors of this article, is provided on page 993.

**V**itamin B<sub>12</sub> (cobalamin) plays an important role in DNA synthesis and neurologic function. Deficiency can lead to a wide spectrum of hematologic and neuropsychiatric disorders that can often be reversed by early diagnosis and prompt treatment.

The true prevalence of vitamin B<sub>12</sub> deficiency in the general population is unknown. The incidence, however, appears to increase with age. In one study,<sup>1</sup> 15 percent of adults older than 65 years had laboratory evidence of vitamin B<sub>12</sub> deficiency. The nearly ubiquitous use of gastric acid-blocking agents, which can lead to decreased vitamin B<sub>12</sub> levels,<sup>2</sup> may have an underappreciated role in the development of vitamin B<sub>12</sub> deficiency. Taking the widespread use of these agents and the aging of the U.S. population into consideration, the actual prevalence of vitamin B<sub>12</sub> deficiency may be even higher than statistics indicate. Despite these facts, the need for universal screening in older adults remains a matter of controversy.<sup>3,4</sup>

## Clinical Manifestations

Vitamin B<sub>12</sub> deficiency is associated with hematologic, neurologic, and psychiatric

manifestations (*Table 1*). It is a common cause of macrocytic (megaloblastic) anemia and, in advanced cases, pancytopenia. Neurologic sequelae from vitamin B<sub>12</sub> deficiency include paresthesias, peripheral neuropathy, and demyelination of the corticospinal tract and dorsal columns (subacute combined systems

TABLE 1  
**Clinical Manifestations  
of Vitamin B<sub>12</sub> Deficiency**

### Hematologic

Megaloblastic anemia  
Pancytopenia (leukopenia, thrombocytopenia)

### Neurologic

Paresthesias  
Peripheral neuropathy  
Combined systems disease (demyelination of dorsal columns and corticospinal tract)

### Psychiatric

Irritability, personality change  
Mild memory impairment, dementia  
Depression  
Psychosis

### Cardiovascular

Possible increased risk of myocardial infarction and stroke

---

*The rightsholder did not grant rights to reproduce this item in electronic media. For the missing item, see the original print version of this publication.*

---

FIGURE 1.

disease). Vitamin B<sub>12</sub> deficiency also has been linked to psychiatric disorders, including impaired memory, irritability, depression, dementia and, rarely, psychosis.<sup>5,6</sup>

In addition to hematologic and neuropsychiatric manifestations, vitamin B<sub>12</sub> deficiency may exert indirect cardiovascular effects. Similar to folic acid deficiency, vitamin B<sub>12</sub> deficiency produces hyperhomocysteinemia, which is an independent risk factor for atherosclerotic disease.<sup>7</sup> Although the role of folic acid supplementation in reducing homocysteine levels as a method for preventing coronary artery disease and stroke contin-

ues to be a subject of great interest, there has been little emphasis on the potential role of vitamin B<sub>12</sub> deficiency as a contributing factor in the development of cardiovascular disease. This possibility becomes especially important when considering vitamin replacement therapy. Folic acid supplementation may mask an occult vitamin B<sub>12</sub> deficiency and further exacerbate or initiate neurologic disease. Therefore, clinicians should consider ruling out vitamin B<sub>12</sub> deficiency before initiating folic acid therapy.<sup>8</sup>

### Normal Absorption of Vitamin B<sub>12</sub>

In humans, only two enzymatic reactions are known to be dependent on vitamin B<sub>12</sub>. In the first reaction, methylmalonic acid is converted to succinyl-CoA using vitamin B<sub>12</sub> as a cofactor (*Figure 1*). Vitamin B<sub>12</sub> deficiency, therefore, can lead to increased levels of serum methylmalonic acid. In the second reaction, homocysteine is converted to methionine by using vitamin B<sub>12</sub> and folic acid as cofactors. In this reaction, a deficiency of vitamin B<sub>12</sub> or folic acid may lead to increased homocysteine levels.

An understanding of the vitamin B<sub>12</sub> absorption cycle helps illuminate the potential causes of deficiency. The acidic environment of the stomach facilitates the breakdown of vitamin B<sub>12</sub> that is bound to food. Intrinsic factor, which is released by parietal cells in the stomach, binds to vitamin B<sub>12</sub> in the duodenum. This vitamin B<sub>12</sub>-intrinsic factor complex subsequently aids in the absorption of vitamin B<sub>12</sub> in the terminal ileum.

In addition to this method of absorption, evidence supports the existence of an alternate system that is independent of intrinsic factor or even an intact terminal ileum. Approximately 1 percent of a large oral dose of vitamin B<sub>12</sub> is absorbed by this second mechanism.<sup>9</sup> This pathway is important in relation to oral replacement. Once absorbed, vitamin B<sub>12</sub> binds to transcobalamin II and is transported throughout the body. The interruption of one or any combination of these steps

---

### The Authors

ROBERT C. OH, CPT, MC, USA, is a staff family physician at U.S. Army Health Clinic in Darmstadt, Germany. Dr. Oh received his medical degree from Boston University School of Medicine and completed residency training in family practice at DeWitt Army Community Hospital in Fort Belvoir, Va.

DAVID L. BROWN, MAJ, MC, USA, is director of primary care sports medicine at Madigan Army Medical Center, Fort Lewis, Wash. He received his medical degree from the Uniformed Services University of the Health Sciences F. Edward Hébert School of Medicine, Bethesda, Md. He completed a residency in family practice at Tripler Army Medical Center, Honolulu, and a fellowship in primary care sports medicine at the Uniformed Services University of Health Sciences.

Address correspondence to Robert C. Oh, CPT, MC, USA, CMR 431, Box 284, APO AE 09175 (e-mail: rob98@yahoo.com). Reprints are not available from the authors.

places a person at risk of developing deficiency (Figure 2).

**Diagnosis of Vitamin B<sub>12</sub> Deficiency**

The diagnosis of vitamin B<sub>12</sub> deficiency has traditionally been based on low serum vitamin B<sub>12</sub> levels, usually less than 200 pg per mL (150 pmol per L), along with clinical evidence of disease. However, studies indicate that older patients tend to present with neuropsychiatric disease in the absence of hematologic findings.<sup>5,6</sup> Furthermore, measurements of metabolites such as methylmalonic acid and

*Elevated levels of methylmalonic acid and homocysteine are a much more sensitive diagnostic clue than a low serum B<sub>12</sub> level in the diagnosis of vitamin B<sub>12</sub> deficiency.*

homocysteine have been shown to be more sensitive in the diagnosis of vitamin B<sub>12</sub> deficiency than measurement of serum B<sub>12</sub> levels alone.<sup>3,10-14</sup>

In a large study<sup>10</sup> of 406 patients with known vitamin B<sub>12</sub> deficiency, 98.4 percent

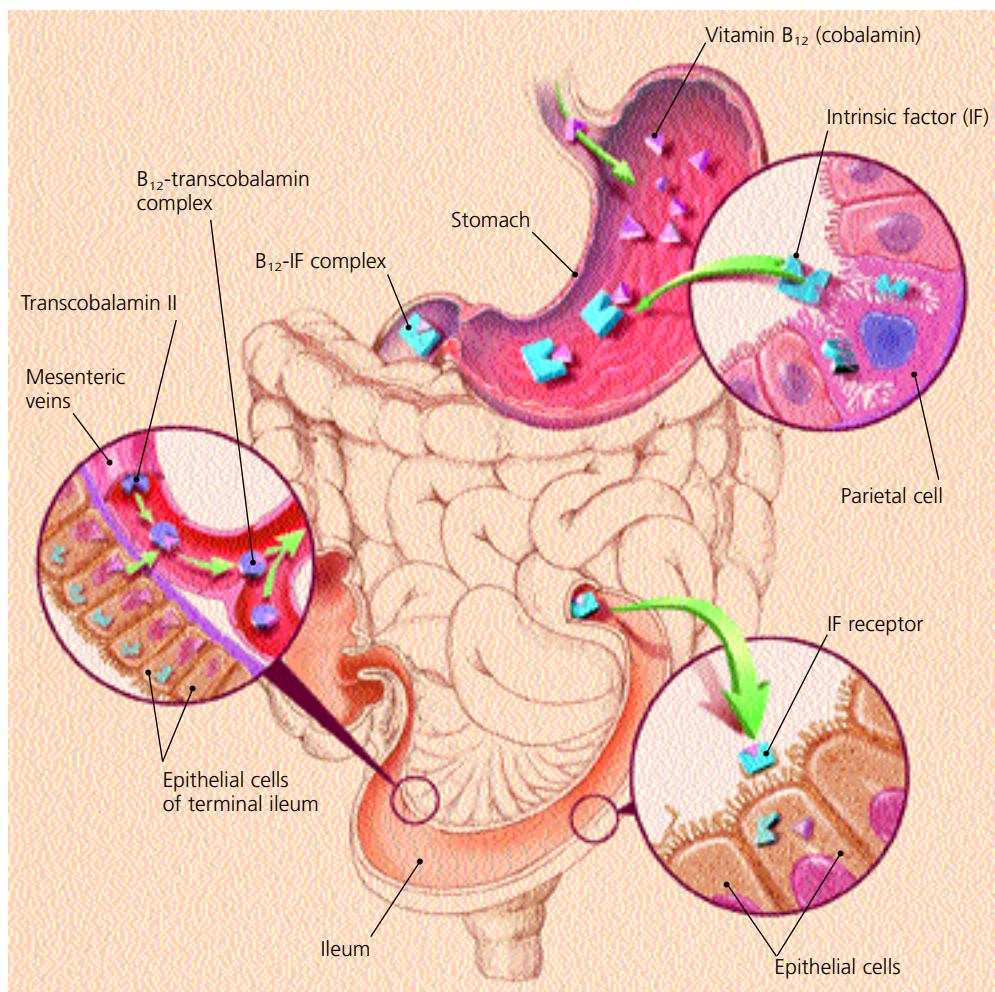


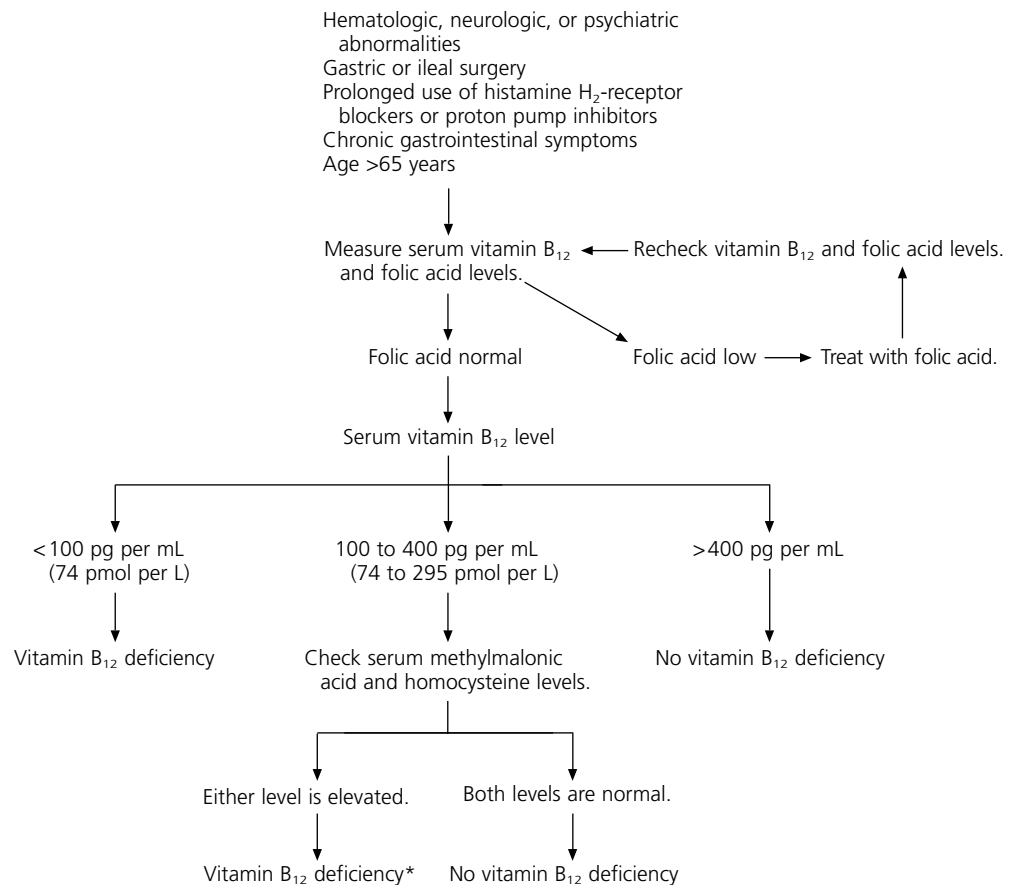
FIGURE 2. Vitamin B<sub>12</sub> absorption and transport.

had elevated serum methylmalonic acid levels, and 95.9 percent had elevated serum homocysteine levels (defined as three standard deviations above the mean). Only one patient out of 406 had normal levels of both metabolites, resulting in a sensitivity of 99.8 percent when methylmalonic acid and homocysteine levels

are used for diagnosis. Interestingly, 28 percent of the patients in this study had normal hematocrit levels, and 17 percent had normal mean corpuscular volumes.

In another study<sup>13</sup> of patients with known pernicious anemia who had not received maintenance vitamin B<sub>12</sub> injections for

### Suspected Vitamin B<sub>12</sub> Deficiency



\*—If levels of metabolites normalize with vitamin B<sub>12</sub> supplementation.

FIGURE 3. Suggested approach to the patient with suspected vitamin B<sub>12</sub> deficiency.

Information from Stabler SP. Screening the older population for cobalamin (vitamin B<sub>12</sub>) deficiency. *J Am Geriatr Soc* 1995;43:1295, and Snow CF. Laboratory diagnosis of vitamin B<sub>12</sub> and folate deficiency. *Arch Intern Med* 1999;159:1297.

months to years, the rise of methylmalonic acid and homocysteine levels was found to precede the decrease in serum vitamin B<sub>12</sub> and the decline in hematocrit. This finding suggests that methylmalonic acid and homocysteine levels can be early markers for tissue vitamin B<sub>12</sub> deficiency, even before hematologic manifestations occur.

Use of methylmalonic acid and homocysteine levels in the diagnosis of vitamin B<sub>12</sub> deficiency has led to some surprising findings. If increased homocysteine or methylmalonic acid levels and a normalization of these metabolites in response to replacement therapy are used as diagnostic criteria for vitamin B<sub>12</sub> deficiency, approximately 50 percent of these patients have serum vitamin B<sub>12</sub> levels above 200 pg per mL.<sup>1</sup> This observation suggests that use of a low serum vitamin B<sub>12</sub> level

*Any process that interferes with gastric acid production, such as prolonged use of acid-suppressing medications, can lead to vitamin B<sub>12</sub> deficiency.*

as the sole means of diagnosis may miss up to one half of patients with actual tissue B<sub>12</sub> deficiency. Other studies have shown similar findings, with the rate of missed diagnosis ranging from 10 to 26 percent when diagnosis is based on low serum vitamin B<sub>12</sub> levels alone.<sup>3</sup>

There are, however, a few caveats to keep in mind. Looking at the reactions that use vitamin B<sub>12</sub> (*Figure 1*),<sup>3</sup> an elevated methylmalonic acid level is clearly more specific for vitamin B<sub>12</sub> deficiency than an elevated homocysteine level. Vitamin B<sub>12</sub> or folic acid deficiency can cause the homocysteine level to rise, so folic acid levels also should be checked in patients with isolated hyperhomocysteinemia.

In addition, folic acid deficiency can cause falsely low serum vitamin B<sub>12</sub> levels. One study<sup>14</sup> revealed that approximately one third of patients with folic acid deficiency had low serum vitamin B<sub>12</sub> levels—less than 100 pg per mL (74 pmol per L) in some patients. Also, methylmalonic acid levels can be elevated in patients with renal disease (the result of decreased urinary excretion); thus, elevated levels must be interpreted with caution.<sup>10</sup>

An algorithm for the diagnosis of vitamin B<sub>12</sub> deficiency is provided in *Figure 3*.<sup>3,14</sup>

### Causes of Vitamin B<sub>12</sub> Deficiency States

Once vitamin B<sub>12</sub> deficiency is confirmed, a search for the etiology should be initiated. Causes of vitamin B<sub>12</sub> deficiency can be divided into three classes: nutritional deficiency, malabsorption syndromes, and other gastrointestinal causes (*Table 2*).<sup>14</sup>

#### NUTRITIONAL DEFICIENCY

Dietary sources of vitamin B<sub>12</sub> are primarily meats and dairy products. In a typical

TABLE 2

### Etiologies of Vitamin B<sub>12</sub> Deficiency

#### Nutritional deficiency

Inadequate intake (e.g., alcoholics, elderly, vegans)

#### Malabsorption syndromes

Food-bound B<sub>12</sub> malabsorption

    Prolonged use of proton pump inhibitors

    Prolonged use of histamine H<sub>2</sub> receptor blockers

Lack of intrinsic factor or parietal cells

    Pernicious anemia

    Atrophic gastritis

    Postgastrectomy

#### Other gastrointestinal causes

Ileal malabsorption

    Enteritis (Crohn's disease)

    Ileal resection

Biologic competition

    Bacterial overgrowth

    Tapeworm infestation

#### Defective transport

Transcobalamin II deficiency

*Adapted with permission from Snow CF. Laboratory diagnosis of vitamin B<sub>12</sub> and folate deficiency. Arch Intern Med 1999;159:1289-98. Copyrighted 1999, American Medical Association.*

*Oral vitamin B<sub>12</sub> replacement is as effective as intramuscular injections, even in patients with pernicious anemia or ileal disease.*

Western diet, a person obtains approximately 5 to 15 mcg of vitamin B<sub>12</sub> daily, much more than the recommended daily allowance of 2 mcg. Normally, humans maintain a large vitamin B<sub>12</sub> reserve, which can last two to five years even in the presence of severe malabsorption.<sup>14</sup> Nevertheless, nutritional deficiency can occur in specific populations. Elderly patients with “tea and toast” diets and chronic alcoholics are at especially high risk. The dietary limitations of strict vegans make them another, less common at-risk population.

#### MALABSORPTION SYNDROMES

The classic disorder of malabsorption is pernicious anemia, an autoimmune disease that affects the gastric parietal cells. Destruction of these cells curtails the production of intrinsic factor and subsequently limits vitamin B<sub>12</sub> absorption. Laboratory evidence of parietal cell antibodies is approximately 85 to 90 percent sensitive for the diagnosis of pernicious anemia. However, the presence of parietal cell antibodies is nonspecific and occurs in other autoimmune states. Intrinsic factor antibody is only 50 percent sensitive, but it is far more specific for the diagnosis of pernicious anemia.

A Schilling test, which distinguishes intrinsic factor-related malabsorption, can be used to diagnose pernicious anemia (Table 3).<sup>14</sup> Specifically, Schilling test results were once used to determine whether a patient required parenteral or oral vitamin B<sub>12</sub> supplementation. This distinction is now unnecessary, because evidence points to a B<sub>12</sub> absorption pathway independent of intrinsic factor, and studies have proved that oral replacement is equal in efficacy to intramuscular therapy.<sup>9</sup> Regardless of the test result, successful treat-

**TABLE 3**  
**Interpretation of the Schilling Test**

<i>Results*</i>	<i>Possible interpretation</i>
Stage 1, normal*	Dietary deficiency Food-bound malabsorption Partial gastrectomy
Stage 1, abnormal; stage 2, normal	Pernicious anemia Gastrectomy Inadequate urine collection in stage 1
Stages 1 and 2, abnormal	Ileal disease or resection Renal insufficiency Inadequate urine collection Bacterial overgrowth syndrome Tapeworm infestation

\*—Stage 1: radiolabeled B<sub>12</sub> administered and 24-hour urine measured for B<sub>12</sub> excretion; the presence of high levels of radiolabeled B<sub>12</sub> in the urine indicates adequate absorption. Stage 2: if stage 1 is abnormal, stage 2 is performed by adding radiolabeled intrinsic factor to B<sub>12</sub> and obtaining another 24-hour urine sample.

Adapted with permission from Snow CF. Laboratory diagnosis of vitamin B<sub>12</sub> and folate deficiency. *Arch Intern Med* 1999;159:1289-98.

ment can still be achieved with oral replacement therapy.

Thus, the utility of the Schilling test has been brought into question.<sup>3</sup> The Schilling test also has fallen out of favor because it is complicated to perform, the radiolabeled vitamin B<sub>12</sub> is difficult to obtain, and interpretation of test results can be problematic in patients with renal insufficiency.

The phenomenon of food-bound malabsorption occurs when vitamin B<sub>12</sub> bound to protein in foods cannot be cleaved and released. Any process that interferes with gastric acid production can lead to this impairment. Atrophic gastritis, with resulting hypochlorhydria, is a major cause, especially in the elderly.<sup>3</sup> Subtotal gastrectomy, once common before the availability of effective medical therapy for peptic ulcer disease, also can lead to vitamin B<sub>12</sub> deficiency by this mechanism.

As mentioned previously, the widespread and prolonged use of histamine H<sub>2</sub>-receptor blockers and proton pump inhibitors for ulcer disease also may cause impaired breakdown of vitamin B<sub>12</sub> from food, causing malabsorption and eventual depletion of B<sub>12</sub> stores. Recent

studies have confirmed that long-term use of omeprazole can lead to lower serum vitamin B<sub>12</sub> levels.<sup>15,16</sup> While more studies are needed to identify the incidence and prevalence of vitamin B<sub>12</sub> deficiency in this subset of patients, screening for subclinical B<sub>12</sub> deficiency should be a consideration in patients who have received long-term acid-suppression therapy.<sup>2</sup>

#### OTHER CAUSES

Other etiologies of vitamin B<sub>12</sub> deficiency, although less common, deserve mention. Patients with evidence of vitamin B<sub>12</sub> deficiency and chronic gastrointestinal symptoms such as dyspepsia, recurrent peptic ulcer disease, or diarrhea may warrant evaluation for such entities as Whipple's disease (a rare bacterial infection that impairs absorption), Zollinger-Ellison syndrome (gastrinoma causing peptic ulcer and diarrhea), or Crohn's disease. Patients with a history of intestinal surgery, strictures, or blind loops may have bacterial overgrowth that can compete for dietary vitamin B<sub>12</sub> in the small bowel, as can infestation with tapeworms or other intestinal parasites. Congenital transport-protein deficiencies, including transcobalamin II deficiency, are another rare cause of vitamin B<sub>12</sub> deficiency.

#### Oral vs. Parenteral Therapy

Because most clinicians are generally unaware that oral vitamin B<sub>12</sub> therapy is effective,<sup>17</sup> the traditional treatment for B<sub>12</sub> deficiency has been intramuscular injections. However, since as early as 1968, oral vitamin B<sub>12</sub> has been shown to have an efficacy equal to that of injections in the treatment of pernicious anemia and other B<sub>12</sub> deficiency states.<sup>9,17-19</sup> Although the majority of dietary vitamin B<sub>12</sub> is absorbed in the terminal ileum through a complex with intrinsic factor, evidence for the previously mentioned alternate transport system is mounting.

In one study,<sup>18</sup> 38 patients with vitamin B<sub>12</sub> deficiency were randomized to receive oral or parenteral therapy. Patients in the parenteral

therapy group received 1,000 mcg of vitamin B<sub>12</sub> intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60, and 90, while those in the oral treatment group received 2,000 mcg daily for 120 days. At the end of 120 days, patients who received oral therapy had significantly higher serum vitamin B<sub>12</sub> levels and lower methylmalonic acid levels than those in the parenteral therapy group. The actual transport mechanism used in this pathway remains unproved, but vitamin B<sub>12</sub> is thought to be absorbed "en masse" in high doses. Surprisingly, one study<sup>20</sup> showed that even in patients who had undergone gastrectomy, vitamin B<sub>12</sub> deficiency could be easily reversed with oral supplementation.

Intramuscular injections, although safe and inexpensive, have several drawbacks. Injections are painful, medical personnel giving the injections are placed at risk of needlestick injuries, and administration of intramuscular injections often adds to the cost of therapy. Treatment schedules for intramuscular administration vary widely but usually consist of initial loading doses followed by monthly maintenance injections. One regimen consists of daily injections of 1,000 mcg for one to two weeks, then a maintenance dose of 1,000 mcg every one to three months.

Although the daily requirement of vitamin B<sub>12</sub> is approximately 2 mcg, the initial oral replacement dosage consists of a single daily dose of 1,000 to 2,000 mcg (Table 4). This high dose is required because of the variable absorption

TABLE 4  
Schedule for Vitamin B<sub>12</sub> Therapy

Route of administration	Initial dosage	Maintenance dosage
Oral	1,000 to 2,000 mcg per day for one to two weeks	1,000 mcg per day for life
Intramuscular	100 to 1,000 mcg every day or every other day for one to two weeks	100 to 1,000 mcg every one to three months

of oral vitamin B<sub>12</sub> in doses of 500 mcg or less.<sup>19</sup> This regimen has been shown to be safe, cost-effective, and well tolerated by patients.<sup>19</sup>

### Follow-Up

After the diagnosis of vitamin B<sub>12</sub> deficiency has been made and a treatment plan has been initiated, follow-up is important to determine the patient's response to therapy. If vitamin B<sub>12</sub> deficiency is associated with severe anemia, correction of the deficiency state should lead to a marked reticulocytosis in one to two weeks. In mild vitamin B<sub>12</sub> deficiency, we recommend repeat measurements of serum vitamin B<sub>12</sub>, homocysteine, and methylmalonic acid levels two to three months after initiating treatment.

*The authors thank Linda L. Brown, M.D., Department of Internal Medicine, Walter Reed Army Medical Center, Washington, D.C., for review of the manuscript.*

*The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.*

*The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army Medical Department or the U.S. Army Service at large.*

### REFERENCES

1. Pennypacker LC, Allen RH, Kelly JP, Matthews LM, Grigsby J, Kaye K, et al. High prevalence of cobalamin deficiency in elderly outpatients. *J Am Geriatr Soc* 1992;40:1197-204.
2. Bradford GS, Taylor CT. Omeprazole and vitamin B<sub>12</sub> deficiency. *Ann Pharmacother* 1999;33:641-3.
3. Stabler SP. Screening the older population for cobalamin (vitamin B<sub>12</sub>) deficiency. *J Am Geriatr Soc* 1995;43:1290-7.
4. Green R. Screening for vitamin B<sub>12</sub> deficiency: caveat emptor [Editorial]. *Ann Intern Med* 1996;124:509-11.
5. Lee GR. Pernicious anemia and other causes of vitamin B<sub>12</sub> (cobalamin) deficiency. In: Lee GR, et al., eds. *Wintrobe's Clinical hematology*. 10th ed. Baltimore: Williams & Wilkins, 1999:941-64.
6. Lindenbaum J, Healton EB, Savage DG, Brust JC, Garrett TJ, Podell ER, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med* 1988;318:1720-8.
7. Nygard O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med* 1997;337:230-6.
8. Tucker KL, Mahnken B, Wilson PW, Jacques P, Selhub J. Folic acid fortification of the food supply. Potential benefits and risks for the elderly population. *JAMA* 1996;276:1879-85.
9. Elia M. Oral or parenteral therapy for B<sub>12</sub> deficiency. *Lancet* 1998;352:1721-2.
10. Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. *Am J Med* 1994;96:239-46.
11. Sumner AE, Chin MM, Abraham JL, Berry GT, Gracely EJ, Allen RH, et al. Elevated methylmalonic acid and total homocysteine levels show high prevalence of vitamin B<sub>12</sub> deficiency after gastric surgery. *Ann Intern Med* 1996;124:469-76.
12. Frenkel EP, Yardley DA. Clinical and laboratory features and sequelae of deficiency of folic acid (folate) and vitamin B<sub>12</sub> (cobalamin) in pregnancy and gynecology. *Hematol Oncol Clin North Am* 2000;14:1079-100.
13. Lindenbaum J, Savage DG, Stabler SP, Allen RH. Diagnosis of cobalamin deficiency: II. Relative sensitivities of serum cobalamin, methylmalonic acid, and total homocysteine concentrations. *Am J Hematol* 1990;34:99-107.
14. Snow CF. Laboratory diagnosis of vitamin B<sub>12</sub> and folate deficiency: a guide for the primary care physician. *Arch Intern Med* 1999;159:1289-98.
15. Marcuard SP, Albernaz L, Khazanie PG. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B<sub>12</sub>). *Ann Intern Med* 1994;120:211-5.
16. Termanini B, Gibril F, Sutliff VE, Yu F, Venzon DJ, Jensen RT. Effect of long-term gastric acid suppressive therapy on serum vitamin B<sub>12</sub> levels in patients with Zollinger-Ellison syndrome. *Am J Med* 1998;104:422-30.
17. Lederle FA. Oral cobalamin for pernicious anemia: back from the verge of extinction. *J Am Geriatr Soc* 1998;46:1125-7.
18. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998;92:1191-8.
19. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret? *JAMA* 1991;265:94-5.
20. Adachi S, Kawamoto T, Otsuka M, Fukao K. Enteral vitamin B<sub>12</sub> supplements reverse postgastrectomy B<sub>12</sub> deficiency. *Ann Surg* 2000;232:199-201.