Vitamin B_{12} Deficiency

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Vitamin B_{12} (cobalamin) deficiency is a common cause of macrocytic anemia and has been implicated in a spectrum of neuropsychiatric disorders. The role of B_{12} deficiency in hyperhomocysteinemia and the promotion of atherosclerosis is only now being explored. Diagnosis of vitamin B_{12} deficiency is typically based on measurement of serum vitamin B_{12} levels; however, about 50 percent of patients with subclinical disease have normal B_{12} levels. A more sensitive method of screening for vitamin B_{12} deficiency is measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B_{12} 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_{12} is a safe and effective treatment for the B_{12} deficiency state. Even when intrinsic factor is not present to aid in the absorption of vitamin B_{12} (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_{12} deficiency, written by the authors of this article, is provided on page 993.

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

Clinical Manifestations

Vitamin B_{12} 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_{12} deficiency include paresthesias, peripheral neuropathy, and demyelination of the corticospinal tract and dorsal columns (subacute combined systems

TABLE 1
Clinical Manifestations of Vitamin B_{12} 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

FIGURE 1.

disease). Vitamin B_{12} deficiency also has been linked to psychiatric disorders, including impaired memory, irritability, depression, dementia and, rarely, psychosis.[5,6]

In addition to hematologic and neuropsychiatric manifestations, vitamin B_{12} deficiency may exert indirect cardiovascular effects. Similar to folic acid deficiency, vitamin B_{12} deficiency produces hyperhomocysteinemia, which is an independent risk factor for atherosclerotic disease.[7] Although the role of folic acid supplementation in reducing homocysteine levels as a method for preventing coronary artery disease and stroke continues to be a subject of great interest, there has been little emphasis on the potential role of vitamin B_{12} 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_{12} deficiency and further exacerbate or initiate neurologic disease. Therefore, clinicians should consider ruling out vitamin B_{12} deficiency before initiating folic acid therapy.[8]

Normal Absorption of Vitamin B_{12}

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

An understanding of the vitamin B_{12} absorption cycle helps illuminate the potential causes of deficiency. The acidic environment of the stomach facilitates the breakdown of vitamin B_{12} that is bound to food. Intrinsic factor, which is released by parietal cells in the stomach, binds to vitamin B_{12} in the duodenum. This vitamin B_{12}–intrinsic factor complex subsequently aids in the absorption of vitamin B_{12} 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_{12} is absorbed by this second mechanism.[9] This pathway is important in relation to oral replacement. Once absorbed, vitamin B_{12} binds to transcobalamin II and is transported throughout the body. The interruption of one or any combination of these steps

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

Elevated levels of methylmalonic acid and homocysteine are a much more sensitive diagnostic clue than a low serum B_{12} level in the diagnosis of vitamin B_{12} deficiency.

Diagnosis of Vitamin B_{12} Deficiency

The diagnosis of vitamin B_{12} deficiency has traditionally been based on low serum vitamin B_{12} 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.[5,6] Furthermore, measurements of metabolites such as methylmalonic acid and homocysteine have been shown to be more sensitive in the diagnosis of vitamin B_{12} deficiency than measurement of serum B_{12} levels alone.[3,10-14]

In a large study[10] of 406 patients with known vitamin B_{12} deficiency, 98.4 percent

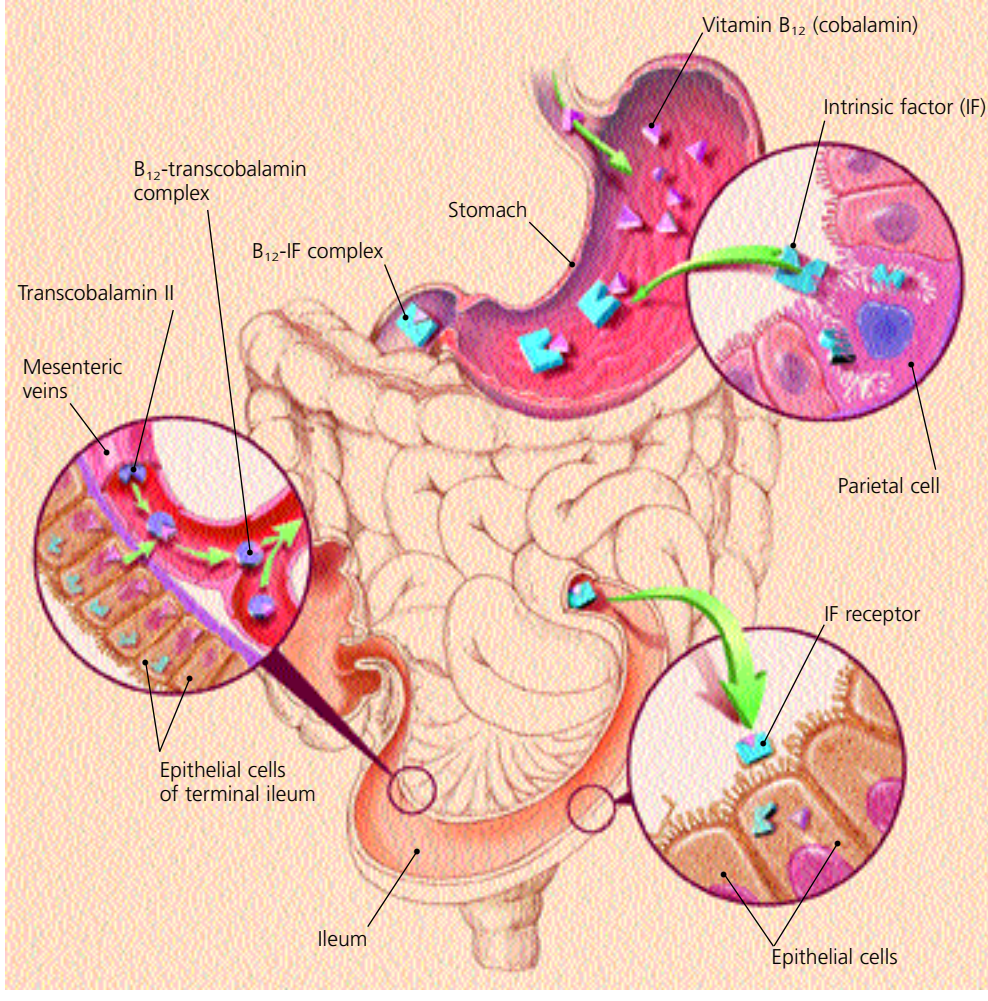
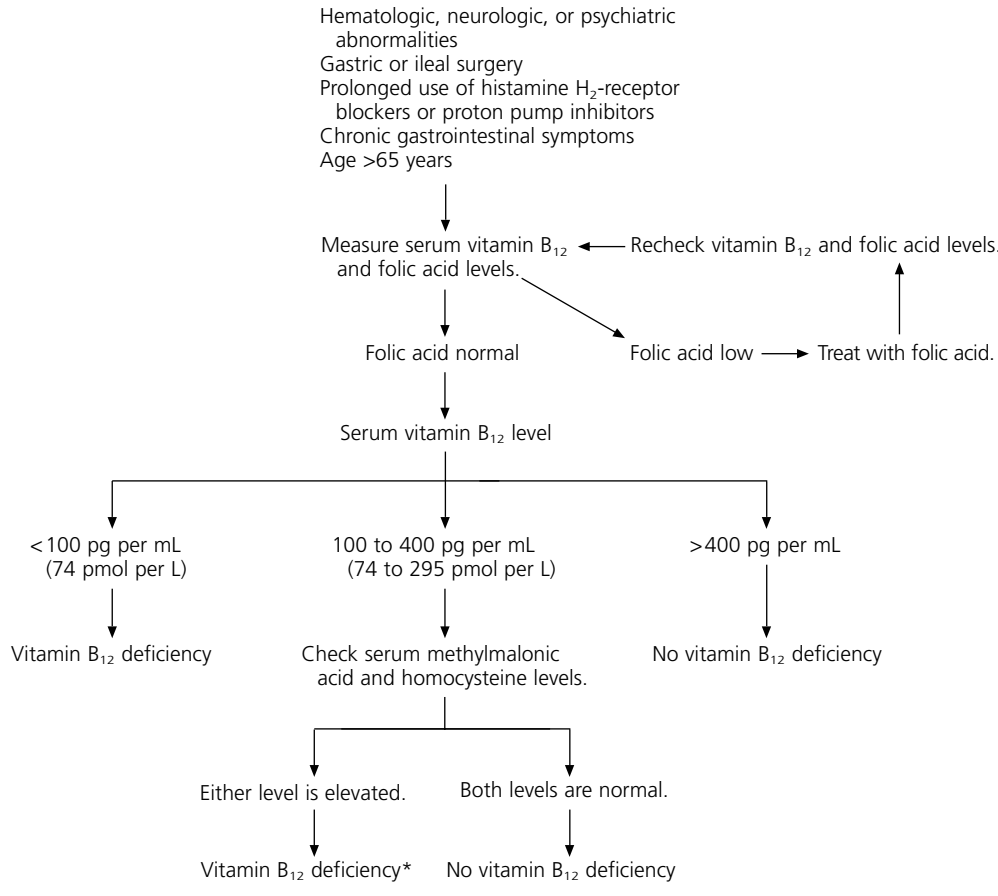


FIGURE 2. Vitamin B_{12} absorption and transport.

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[13] of patients with known pernicious anemia who had not received maintenance vitamin B_{12} injections for



—If levels of metabolites normalize with vitamin B_{12} supplementation.

FIGURE 3. Suggested approach to the patient with suspected vitamin B_{12} deficiency.

Information from Stabler SP. Screening the older population for cobalamin (vitamin B_{12}) deficiency. J Am Geriatr Soc 1995:43:1295, and Snow CF. Laboratory diagnosis of vitamin B_{12} 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_{12} and the decline in hematocrit. This finding suggests that methylmalonic acid and homocysteine levels can be early markers for tissue vitamin B_{12} deficiency, even before hematologic manifestations occur.

Use of methylmalonic acid and homocysteine levels in the diagnosis of vitamin B_{12} 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_{12} deficiency, approximately 50 percent of these patients have serum vitamin B_{12} levels above 200 pg per mL.[1] This observation suggests that use of a low serum vitamin B_{12} level as the sole means of diagnosis may miss up to one half of patients with actual tissue B_{12} 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_{12} levels alone.[3]

Any process that interferes with gastric acid production, such as prolonged use of acid-suppressing medications, can lead to vitamin B_{12} deficiency.

There are, however, a few caveats to keep in mind. Looking at the reactions that use vitamin B_{12} *(Figure 1)*,[3] an elevated methylmalonic acid level is clearly more specific for vitamin B_{12} deficiency than an elevated homocysteine level. Vitamin B_{12} 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_{12} levels. One study[14] revealed that approximately one third of patients with folic acid deficiency had low serum vitamin B_{12} 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.[10]

An algorithm for the diagnosis of vitamin B_{12} deficiency is provided in *Figure 3*.[3,14]

TABLE 2
Etiologies of Vitamin B_{12} Deficiency

Nutritional deficiency
Inadequate intake (e.g., alcoholics, elderly, vegans)
Malabsorption syndromes
Food-bound B_{12} malabsorption
Prolonged use of proton pump inhibitors
Prolonged use of histamine H_2 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_{12} and folate deficiency. Arch Intern Med 1999;159:1289-98. Copyrighted 1999, American Medical Association.

Causes of Vitamin B_{12} Deficiency States

Once vitamin B_{12} deficiency is confirmed, a search for the etiology should be initiated. Causes of vitamin B_{12} deficiency can be divided into three classes: nutritional deficiency, malabsorption syndromes, and other gastrointestinal causes *(Table 2)*.[14]

NUTRITIONAL DEFICIENCY

Dietary sources of vitamin B_{12} are primarily meats and dairy products. In a typical

Oral vitamin B_{12} 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_{12} daily, much more than the recommended daily allowance of 2 mcg. Normally, humans maintain a large vitamin B_{12} reserve, which can last two to five years even in the presence of severe malabsorption.[14] 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.

TABLE 3
Interpretation of the Schilling Test

*Results**	*Possible interpretation*
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_{12} administered and 24-hour urine measured for B_{12} excretion; the presence of high levels of radiolabeled B_{12} in the urine indicates adequate absorption. Stage 2: if stage 1 is abnormal, stage 2 is performed by adding radiolabeled intrinsic factor to B_{12} and obtaining another 24-hour urine sample.*

Adapted with permission from Snow CF. Laboratory diagnosis of vitamin B_{12} and folate deficiency. Arch Intern Med 1999;159:1289-98.

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_{12} 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)*.[14] Specifically, Schilling test results were once used to determine whether a patient required parenteral or oral vitamin B_{12} supplementation. This distinction is now unnecessary, because evidence points to a B_{12} absorption pathway independent of intrinsic factor, and studies have proved that oral replacement is equal in efficacy to intramuscular therapy.[9] Regardless of the test result, successful treatment can still be achieved with oral replacement therapy.

Thus, the utility of the Schilling test has been brought into question.[3] The Schilling test also has fallen out of favor because it is complicated to perform, the radiolabeled vitamin B_{12} 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_{12} 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.[3] Subtotal gastrectomy, once common before the availability of effective medical therapy for peptic ulcer disease, also can lead to vitamin B_{12} deficiency by this mechanism.

As mentioned previously, the widespread and prolonged use of histamine H_2-receptor blockers and proton pump inhibitors for ulcer disease also may cause impaired breakdown of vitamin B_{12} from food, causing malabsorption and eventual depletion of B_{12} stores. Recent

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

OTHER CAUSES

Other etiologies of vitamin B_{12} deficiency, although less common, deserve mention. Patients with evidence of vitamin B_{12} 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_{12} 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_{12} deficiency.

Oral vs. Parenteral Therapy

Because most clinicians are generally unaware that oral vitamin B_{12} therapy is effective,[17] the traditional treatment for B_{12} deficiency has been intramuscular injections. However, since as early as 1968, oral vitamin B_{12} has been shown to have an efficacy equal to that of injections in the treatment of pernicious anemia and other B_{12} deficiency states.[9,17-19] Although the majority of dietary vitamin B_{12} 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,[18] 38 patients with vitamin B_{12} deficiency were randomized to receive oral or parenteral therapy. Patients in the parenteral therapy group received 1,000 mcg of vitamin B_{12} 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_{12} 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_{12} is thought to be absorbed "en masse" in high doses. Surprisingly, one study[20] showed that even in patients who had undergone gastrectomy, vitamin B_{12} 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_{12} 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_{12} 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_{12} in doses of 500 mcg or less.[19] This regimen has been shown to be safe, cost-effective, and well tolerated by patients.[19]

Follow-Up

After the diagnosis of vitamin B_{12} 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_{12} 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_{12} deficiency, we recommend repeat measurements of serum vitamin B_{12}, 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_{12} deficiency. Ann Pharmacother 1999;33:641-3.
3. Stabler SP. Screening the older population for cobalamin (vitamin B_{12}) deficiency. J Am Geriatr Soc 1995;43:1290-7.
4. Green R. Screening for vitamin B_{12} deficiency: caveat emptor [Editorial]. Ann Intern Med 1996; 124:509-11.
5. Lee GR. Pernicious anemia and other causes of vitamin B_{12} (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_{12} deficiency. Lancet 1998;352:1721-2.
10. Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine derterminations for diagnosing cobalamin and folate deficiencies. Am J Med 1994;96:239-46.
11. Sumner AE, Chin MM, Abrahm JL, Berry GT, Gracely EJ, Allen RH, et al. Elevated methylmalonic acid and total homocysteine levels show high prevalence of vitamin B_{12} 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_{12} (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_{12} 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_{12}). 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_{12} 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_{12} supplements reverse postgastrectomy B_{12} deficiency. Ann Surg 2000;232:199-201.