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Vitamin B_{12}

DESCRIPTION

The term vitamin B_{12} (cobalamin) is used in two different ways. Vitamin B_{12}, a member of the B-vitamin family, is a collective term for a group of cobalt-containing compounds known as corrinoids. The principal cobalamins are cyanocobalamin, hydroxocobalamin and the two coenzyme forms of vitamin B_{12}, methylcobalamin and 5-deoxyadenosylcobalamin (adenosylcobalamin). The term vitamin B_{12} is more commonly used to refer to only one of these forms, cyanocobalamin. Cyanocobalamin is the principal form of the vitamin used for fortification of foods and in nutritional supplements. In this monograph, vitamin B_{12} will be used in both ways. The meaning will be clear from its context. The cobalamins are comprised of a nucleotide (base, ribose and phosphate) attached to a corrin ring. The corrin ring is made up of four pyrrole groups and an atom of cobalt in its center. The cobalt atom attaches to a methyl group, a deoxyadenosyl group, a hydroxyl group or a cyano group, to yield the four cobalamin forms mentioned above.

Vitamin B_{12} is the most chemically complex of all the vitamins. It is also one of the most biologically interesting ones. Because of the striking dark red color of its crystals, vitamin B_{12} has been called "nature's most beautiful cofactor." Its close relatives hemoglobin, chlorophyll and the cytochromes are also brightly colored complex organometallic substances, which, along with vitamin B_{12} and some others derived from the parent molecule called uroporphyrinogen III, have led to their being known as the pigments of life. Vitamin B_{12} works in close partnership with folate in the synthesis of the building blocks for DNA and RNA synthesis as well as the synthesis of molecules important for the maintenance of the integrity of the genome. It is also essential for the maintenance of the integrity of the nervous system and for the synthesis of molecules which are involved in fatty acid biosynthesis and the production of energy. The human body does all of this with just two to three milligrams of the vitamin, which is much less than the weight of a tenth of a drop of water. It is even speculated that B_{12} was mainly responsible for the origin of the DNA world from the RNA world.

Deficiency of vitamin B_{12} results in hematological, neurological and gastrointestinal effects. The hematological effects of the deficiency are identical to that of folate deficiency and are caused by interference with DNA synthesis. The hematologic symptoms and signs of B_{12} deficiency, include hypersegmentation of polymorphonuclear leukocytes, macrocytic, hyperchromic erythrocytes, elevated mean corpuscular volume (MCV), elevated mean corpuscular hemoglobin concentration (MCH, MCHC), a decreased red blood cell count, pallor of the skin, decreased energy and easy fatigability, shortness of breath and palpitations. The resulting anemia of B_{12} deficiency, as is the case of the anemia of folate deficiency, is a megaloblastic macrocytic anemia. However, in the context of a simultaneous iron deficiency anemia, which is a microcytic one, anemia secondary to B_{12} deficiency may not result in macrocytic erythrocytes.

The neurological effects of the vitamin deficiency may occur even in the absence of anemia. This is particularly true in those who are over 60 years old. Vitamin B_{12} deficiency principally affects the peripheral nerves, and in later stages, the spinal cord. The symptoms and signs of the neurological effects of B_{12} deficiency, include tingling and numbness in the extremities (particularly the lower extremities), loss of vibratory and position sensation, abnormalities of gait, spasticity, Babinski's responses, irritability, depression and cognitive changes (loss of concentration, memory loss, dementia). Visual disturbances, impaired bladder and bowel control, insomnia and impotence may also occur. Gastrointestinal effects of B_{12} deficiency, include intermittent diarrhea and constipation, abdominal pain, flatulence and burning of the tongue (glossitis). Anorexia and weight loss are general symptoms of B_{12} deficiency. Recently, age-related hearing loss has been associated with poor vitamin B_{12} and folate status. Poor B_{12} status has also been associated with Alzheimer's disease.

Pernicious anemia is the most common cause of clinical B_{12} deficiency in temperate regions. Pernicious anemia is the result of an autoimmune process in which parietal cell autoantibodies against the gastric H^+/K^+-adenosine triphosphatase (the gastric proton pump) cause loss of gastric parietal cells. The loss of parietal cells results in diminished production of the intrinsic factor. The intrinsic factor is necessary for B_{12} absorption (see Pharmacokinetics). Deficiency of intrinsic factor results in B_{12} deficiency. Inadequate B_{12} intake is another cause of B_{12} deficiency. Breastfed infants of vegan mothers are particularly at risk for B_{12} deficiency. Total gastrectomy results in B_{12} deficiency secondary to lack of intrinsic factor. Pancreatic insufficiency and atrophic gastritis result in B_{12} deficiency secondary to inability to digest dietary protein-bound B_{12}. Small bowel disorders, including ileal resection or bypass, Crohn's disease, malignancy, tropical sprue, celiac sprue (gluten-induced enteropathy) and amyloidosis result in B_{12} deficiency secondary to decreased absorption of the vitamin. Bacterial overgrowth of the small intestine results in B_{12} deficiency secondary to bacterial competition for uptake of the vitamin. Certain drugs, including proton pump inhibitors can interfere with absorption of the vitamin (see Interactions). Nitrous oxide anesthesia can cause a functional B_{12} deficiency via degradation of B_{12} coenzymes (see Interactions). Rare congenital disorders such as transcobalamin II deficiency and defective intrinsic factor production result in B_{12} deficiency. Finally, infestation with the tapeworm *Diphyllobothrium latum* can cause B_{12} deficiency secondary to competition for uptake of B_{12} by the parasite. In this regard, in the early 1900s, B_{12} deficiency was common in Jewish women in the United States who prepared their own gefilte fish. They used fresh-water fish, including pike, pickeral and carp, which hosted the wormlike larvae of the parasite. The women would sample the fish, by tasting it, from the time it was quite raw until it was well cooked. Although their children totally enjoyed the prepared gefilte fish, the Jewish mothers wound up with forty-foot parasites in their digestive tracts and B_{12} deficiencies.

The two coenzyme forms of vitamin B_{12} are methylcobalamin and 5'-deoxyadenosylcobalamin (adenosylcobalamin). Methylcobalamin is a cofactor for the enzyme methionine synthase, while adenosycobalamin is a cofactor for the enzyme L-methylmalonyl coenzyme A (methylmalonyl-CoA) mutase. Methionine synthase is one of the key enzymes in intermediary metabolism. It catalyzes the conversion of homocysteine to methionine. Its folate partner in the reaction is 5-methyltetrahydrofolate (intracellular folates are present in their polyglutamate forms). This is the only reaction in the body in which folate and B_{12} are coparticipants. In addition to forming methionine, 5-methyltetrahydrofolate is converted to tetrahydrofolate. The reactions occur in the following manner: methylcobalamin transfers its methyl group to homocysteine yielding methionine and 5-methyltetrahydrate transfers its methyl group to cobalamin reconverting it to methylcobalamin. Methionine is converted to S-adenosylmethionine (SAMe), the major donor of methyl groups in transmethylation reactions, including reactions that are involved in the synthesis of basic myelin basic protein.

Tetrahydrofolate is converted to 5,10-methylenetetrahydrofolate via the action of the enzyme serine hydroxymethyltransferase. 5,10-Methylenetetrahydrofolate is presented with three metabolic opportunities. It can be converted to 5-methyltetrahydrofolate—the folate cofactor of the methionine synthase reaction—via the enzyme 5,10-methylenetetrahydrofolate reductase; it can transfer its one-carbon residue to deoxyuridylic acid to form thymidylic acid or it can be converted to 5-formyltetrahydrofolate, which is a one-carbon donor in the *de novo* synthesis of purine nucleotides.

The hematological effects of B_{12} deficiency are accounted for as follows: B_{12} deficiency leads to reduced synthesis of tetrahydrofolate as well as methionine. Decreased tetrahydrofolate results in decreased 5,10-methylenetetrahydrofolate which in turn, results in decreased conversion of deoxuridylate to thymidylate and decreased *de novo* synthesis of purine nucleotides. In addition, because of decreased synthesis of methionine and S-adenosylmethionine, the enzyme 5,10-methylenetetrahydrofolate reductase converts most of the 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the so-called methyl trap. To summarize, decreased B_{12} results in a decrease in the nucleotide precursor pool for DNA synthesis (thymidylic acid, purine nucleotides) which results in decreased DNA replication and cell division and finally to a megaloblastic anemia. Since the megaloblastic anemia induced by B_{12} deficiency is caused by a functional cellular folate deficiency, it is not surprising that it can be corrected with administration of folate. On the other hand, the neurological deficits of vitamin B_{12} deficiency can not be corrected with folate administration. Further, high doses of folate administered to those with an undiagnosed B_{12} deficiency can cause progression of neurological symptoms.

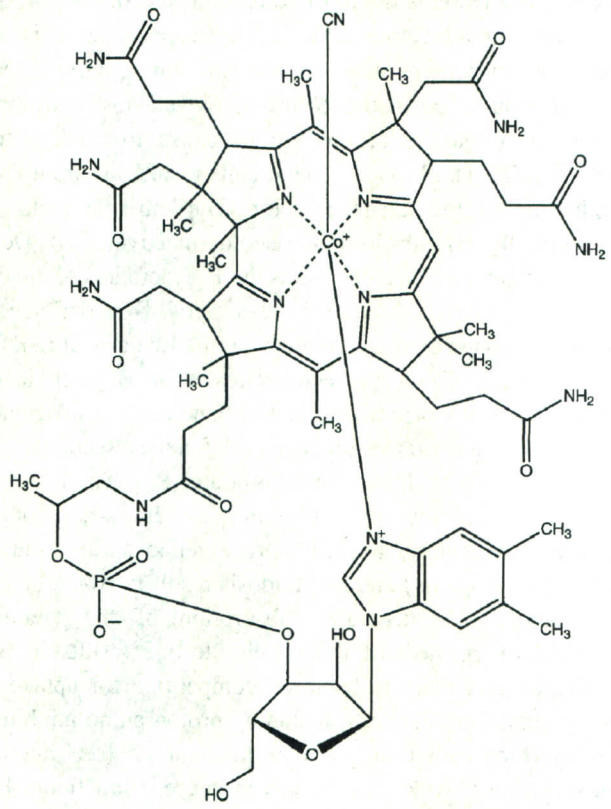
The neurological effects of B_{12} deficiency are accounted for as follows: Consequences of B_{12} deficiency, in addition to those mentioned above, include increased serum levels of homocysteine, decreased levels of methionine and S-adenosylmethionine and a decreased ratio of S-adenosylmethionine to S-adenosylhomocysteine, the product of S-adenosylmethionine methyltransferase reactions. Decreased S-adenosylmethionine in the central nervous system results in decreased methylation reactions and an overall state of hypomethylation. Transmethylation reactions are important in the synthesis of a number of substances in the central

nervous system, including myelin basic protein which is involved in the process of myelination. Much research is needed to better elucidate the mechanism of the neurological effects of B_{12} deficiency.

In addition to methionine synthase, B_{12} is a cofactor in the methylmalonyl-CoA mutase reaction. In this reaction, the coenzyme form of B_{12} is adenosylcobalamin. A number of substances, including the branched-chain amino acids isoleucine and valine, as well as methionine, threonine, thymine and odd-chain fatty acids are metabolized via methylmalonyl semialdehyde or propionyl-CoA to methylmalonyl-CoA. Methylmalonyl-CoA mutase converts methylmalonyl-CoA to succinyl-CoA. This occurs in the mitochondria. Succinyl-CoA can be metabolized in the tricarboxylic acid cycle to produce energy and it is also involved in the synthesis of fatty acids. Methylmalonic acid is elevated in the serum and urine in those with B_{12} deficiency.

Animal products are the principal food sources of vitamin B_{12}. B_{12} cannot be made by plants or by animals. It is thought that only bacteria (eubacteria, archaebacteria) manufacture the vitamin. The B_{12} in animal products is derived from bacterial B_{12} sources. The richest dietary sources of cobalamin are the liver, brain and kidney. Other sources, include egg yolk, clams, oysters, crabs, sardines, salmon and heart. Lower amounts of cobalamin are found in fish, beef, lamb, pork, chicken, cheese and milk. Plant foods are generally devoid of B_{12}. Some fermented plant products, e.g., tempeh, may have some vitamin B_{12}. Pseudovitamin B_{12} refers to B_{12}-like substances which are found in certain organisms, such as *Spirulina* spp. (blue-green algae, cyanobacteria). However, these substances do not have B_{12} biological activity for humans. Food-form B_{12} is comprised of protein-bound methylcobalamin and adenosylcobalamin.

Vitamin B_{12}, B_{12} and cobalamin are terms that are used interchangeably. Vitamin B_{12} most commonly refers to one of the cobalamin forms, cyanocobalamin. Cyanocobalamin is also known as 5,6-dimethylbenzimidazolyl cyanocobamide. Its molecular formula is $C_{63}H_{88}CoN_{14}O_{14}P$ and its molecular weight is 1355.38 daltons. The structural formula is:



Vitamin B_{12}

ACTIONS AND PHARMACOLOGY

ACTIONS

Vitamin B_{12} is used in the treatment of B_{12} deficiency states, including megaloblastic anemia. It may have antiatherogenic, neuroprotective, anticarcinogenic and detoxifying activities. B_{12} has putative anti-allergic and mood-modulatory activities.

MECHANISM OF ACTION

Vitamin B_{12}, in the form of methylcobalamin, is a cofactor in the methionine synthase reaction. The enzyme converts homocysteine to methionine. Folate, in the form of 5-methyltetrahydrofolate (as the pentaglutamate) is the other cofactor in the reaction. In addition to methionine, tetrahydrofolate (again, as the pentaglutame) is also formed. Tetrahydrofolate is converted to 5,10-methylenetetrahydrofolate which is a cofactor in the formation of thymidylic acid from deoxyuridylic acid and which is also converted to 5-formyltetrahydrofolate, a one-carbon donor in the *de novo* synthesis of purine nucleotides. B_{12} deficiency results in decreased formation of thymidylic acid and purine nucleotides, precursors of DNA synthesis and which are necessary for normal cell division. Megaloblastic anemia is the consequence of this and administration of B_{12}, which yields the B_{12} cofactor for methionine synthase, corrects this problem. Methionine is a precursor of S-adenosylmethionine

(SAMe). SAMe is the principal transmethylating agent and is involved in, among many other things, the synthesis of myelin basic protein. Abnormal myelin basic protein resulting in defective myelination, is thought to be responsible for many of the neurological effects of B_{12} deficiency. The neurological effects may or may not be corrected with administration of B_{12} in those with B_{12} deficiency. Whether the neurological effects are reversible after treatment depends on their duration.

Hyperhomocysteinemia is thought to be an independent risk factor for coronary heart disease and other vascular disorders. B_{12} works in concert with folate in the methionine synthase reaction, which metabolizes homocysteine to methionine. This is a key reaction in the maintenance of low serum homocysteine levels. The mechanism by which elevated homocysteine levels might increase the risk of developing vascular disease is unclear. It has been shown that homocysteine increases platelet adhesiveness, promotes the growth of smooth muscle cells and causes endothelial dysfunction. Homocysteine may also promote oxidative stress resulting in, among other things, the oxidation of low-density lipoproteins (LDL) to oxidized-LDL. All of these possible activities of homocysteine can play roles in atherogenesis.

B_{12} deficiency can result in a number of neurological effects, including peripheral neuropathy and cognitive changes, including memory loss and dementia. Administration of B_{12} successfully reverses mild memory impairment and peripheral neuropathy, if not advanced neurological deficits, in most elderly subjects deficient in the vitamin. The mechanism by which B_{12} deficiency causes neurological effects and by which B_{12} administration may reverse them is not well understood. B_{12} and folate are cofactors in the conversion of homocysteine to methionine and methionine is the precursor of the transmethylating agent S-adenosylmethionine (SAMe). SAMe is involved in the synthesis of myelin basic protein which can become defective in the context of B_{12} deficiency. Defective myelin basic protein and resultant defective myelination can account, in large part, for the peripheral neuropathy of B_{12} deficiency. Hyperhomocysteinemia, another consequence of B_{12} deficiency, may also contribute to the neurological effects of deficiency of the vitamin. Elevated homocysteine levels may cause cerebrovascular effects which could lead to cognitive changes. Decreased brain levels of SAMe may result in disturbances in certain neurotransmitters. SAMe is involved in key methylation reactions in catecholamine synthesis and metabolism in the brain. These neurotransmitters are known to be important in maintaining the affective state. In the elderly, depression often presents as cognitive changes, including dementia.

Vitamin B_{12} deficiency has been associated with Alzheimer's disease, at least in some with this neurodegenerative disorder. It is hypothesized that the altered B_{12} status that may occur in those with the disorder is due, in part, to a defect in the protein megalin. Megalin is a member of the low-density lipoprotein receptor family, and mediates the ileal uptake of the cubulin-bound B_{12}-intrinsic factor complex (see Pharmacokinetics). The low-density lipoprotein receptors include receptors that bind apolipoprotein E, amyloid precursor protein and $alpha_2$-macroglobulin, substances that have been linked to Alzheimer's disease. Impaired transport of B_{12} to the central nervous system may, in part, account for the pathogenesis of the disorder.

There is some evidence, mainly epidemiological, that B_{12} may protect against certain types of cancer. A couple of clinical studies have shown that a combination of B_{12} and folic acid significantly reduces the number of abnormal bronchial cells thought to be cancer cell precursors. The mechanism of the possible anticarcinogenic effect of B_{12} is unclear. B_{12} deficiency results in decreased levels of SAMe and thymidylic acid, as discussed above. SAMe, among other things, is involved in DNA methylation which results in regulation of its genetic expression via a process known as gene silencing. Abnormal DNA methylation patterns are characteristic of neoplastic cells. Decreased SAMe and thymidylic acid levels may also lead to increased errors in DNA replication, increased DNA strand breaks and defective DNA repair.

Hydroxocobalamin is used in conditions which are associated with cyanide toxicity, such as may occur with sodium nitroprusside therapy and Leber's optic atrophy. Hydroxocobalamin is used parenterally in these cases; it combines with cyanide to form cyanocobalamin. Clearly, cyanocobalamin is not the right form of B_{12} for use in these conditions. B_{12} can also combine with sulfite and has been found to be effective in the management of sulfite-induced hypersensitivity conditions in some preliminary studies. The studies used cyanocobalamin. Perhaps better results could have been obtained with hydroxocobalamin. There is no evidence that B_{12} has any effect in the management of other hypersensitive or allergic conditions.

Vitamin B_{12} may have mood-modulatory activity in some, e.g., the elderly, who are B_{12} deficient. There is no evidence that B_{12} has mood-modulatory activity in those who are not deficient in the vitamin. As discussed above, SAMe is involved in key methylation reactions in catecholamine synthesis in the brain and these neurotransmitters are known to be important in maintaining the affective state.

PHARMACOKINETICS

Vitamin B_{12} is found naturally in food sources (principally animal products) in protein-bound forms. Cyanocobalamin is the principal form of vitamin B_{12} used in nutritional supplements and for fortification of foods. Methylcobalamin is also available for nutritional supplementation and hydroxocobalamin is available for parenteral administration.

Naturally found B_{12} is dissociated from proteins in the stomach via the action of acid and the enzyme pepsin. The forms of B_{12} released by this process are methylcobalamin and adenosylcobalamin. All forms of B_{12} bind to proteins called haptocorrins or R proteins, which are secreted by the salivary glands and the gastric mucosa. This binding occurs in the stomach. Pancreatic proteases partially degrade the B_{12}-haptocorrin complexes in the small intestine where the B_{12} that is released then binds to intrinsic factor (IF). Intrinsic factor is a glycoprotein which is secreted by gastric parietal cells. The B_{12}-intrinsic factor complex is absorbed from the terminal ileum into the ileal enterocytes via a process that first requires the complex to bind to a receptor called cubilin. Within the enterocytes, B_{12} is released from the B_{12}-IF complex and then binds to another protein called transcobalamin II which delivers it to the portal circulation. The portal circulation transports B_{12} to the liver which takes up about 50% of the vitamin; the reminder is transported to the other tissues of the body via the systemic circulation.

Vitamin B_{12} in the circulation is bound to the plasma proteins transcobalamin I (TCI), transcobalamin II (TCII) and transcobalamin III (TCIII). Approximately 80% of plasma B_{12} is bound to TCI. TCII is the principal B_{12} binding protein for the delivery of B_{12} to cells, via specific receptors for TCII. This B_{12} binding protein (TCII) is identical to the one that delivers B_{12} from the enterocytes to the portal circulation (see above).

Total absorption increases with increased intake of the vitamin. However, the absorption efficacy of the vitamin decreases with increased dosage. Studies with cyanocobalamin found that 50% of the vitamin was absorbed at a dose of one microgram, 20% at a dose of 5 micrograms and about 5% at a dose of 25 micrograms. Significantly, very large doses of B_{12} are absorbed with an absorption efficiency of about one percent. This occurs via passive diffusion even in the absence of intrinsic factor. Thus, large oral doses may be given for the treatment of B_{12} deficiency instead of using the parenteral route (usually, intramuscularly). There are now several studies confirming this. The absorption efficiency of B_{12} from foods is approximately 50%.

The vitamin B_{12}-transcobalamin II complex is degraded intracellularly via lysosomal proteases to yield cobalamin (cyanocobalamin, methylcobalamin, adenosylcobalamin, hydroxocobalamin). Cobalamin is metabolized to methylcobalamin in the cytosol and to adenosylcobalamin in the mitochondria. Methylcobalamin is the principal circulating form of cobalamin. Adenosylcobalamin comprises more than 70% of cobalamin in the liver, erythrocytes, kidney and brain. The total body content of cobalamin ranges from two to three milligrams, with approximately 50% of it residing in the liver.

Vitamin B_{12} is secreted in the bile and reabsorbed via the enterohepatic circulation. Some of the B_{12} secreted in the bile is excreted in the feces. Also, oral B_{12} that is not absorbed is excreted in the feces. Reabsorption of B_{12} via the enterohepatic circulation requires the intrinsic factor. If the circulating level of B_{12} exceeds the B_{12} binding capacity of the blood, a situation that usually occurs following parenteral administration of the vitamin, the excess is excreted in the urine.

INDICATIONS AND USAGE

Vitamin B_{12} is of such vital nutritional importance that some authorities have recently called for mandatory fortification of some foods with this vitamin. Vitamin B_{12} is indicated in those with vitamin B_{12} deficiency. It is especially important for the elderly and for those who have had gastric surgery. Both groups are at high risk for vitamin B_{12} deficiency. There is evidence that it may be beneficial in some others with low vitamin B_{12} status and in some with malabsorption of B_{12}, including some who are chronically ill, as well as some vegetarians, among others. There is some preliminary indication that vitamin B_{12} may be helpful in inhibiting a pre-cancerous condition in the lungs of smokers, that it might help ameliorate the symptoms of some neuropsychiatric disorders and that it might be useful in some with chronic fatigue and HIV disease. It has been suggested that vitamin B_{12} might help prevent some vascular diseases and breast cancer, based upon epidemiological and theoretical considerations. Claims that it is a general "energizer" are anecdotal. There is some evidence that vitamin B_{12} can protect against hypersensitivity to sulfites. Earlier open trials suggested that methylcobalamin was effective in the management of sleep-wake rhythm disorders. However, a recent double-blind controlled trial with this form of B_{12} failed to confirm this. A recent study has associated low vitamin B_{12} status with brain atrophy/shrinkage and subsequent cognitive impairment in the elderly.

RESEARCH SUMMARY

Clinically, overt vitamin B_{12} deficiency manifests as megaloblastic anemia and neurologic dysfunction. There are more clinically silent and subtle forms of cobalamin deficiency which are also reversible with vitamin B_{12} therapy. In addition, mild deficiency may be present in a number of populations, including, most significantly, the elderly. It is

estimated that 10-15% of those over 60 have vitamin B_{12} deficiency, due, principally, to decreased absorption of naturally occurring vitamin B_{12} caused by an age-related atrophic gastritis that diminishes the acid-pepsin secretions that normally release free vitamin B_{12} from food proteins.

An editorial in the *American Journal of Clinical Nutrition* recently suggested that the time may be fast approaching when mandatory fortification of some foods with vitamin B_{12} will be deemed appropriate. The editorialists note that data from the U.S. National Health and Nutrition Examination Survey (NHANES) "indicate that the function of vitamin B_{12} deteriorates as serum folate status increases in persons who are deficient in vitamin B_{12}. More seriously, the data show that persons with both low vitamin B_{12} and high folate concentrations were at particularly high risk of memory impairment and anemia." Thus a very significant proportion of the elderly could be at high risk of cognitive impairment because of an imbalance between folate and vitamin B_{12}. This is of special concern because since 1998 mandatory folic acid fortification has been in effect in the United States, Canada and more than 50 other countries, largely for the purpose of reducing the incidence of neural tube defects in the unborn. Folate fortification is useful, but if it creates a harmful imbalance with respect to vitamin B_{12}, the editorialists argue, then the need for concurrent mandatory vitamin B_{12} fortification becomes more urgent. They also point out that whereas neural tube defects are a relatively rare event in pregnancies (1 per 1,000), the negative sequelae of vitamin B_{12} deficiency are comparatively enormous, including not only increased cognitive dysfunction but also increased incidence of anemia, breast cancer and possibly diabetes in the offspring, among others. There is also the problem, they point out, that folic acid can mask vitamin B_{12} deficiency by preventing anemia but not neurological damage. Irrespective of folic acid fortification, they suggest that vitamin B_{12} fortification will benefit vegetarians, breastfed infants and the elderly, all of whom are at high risk for deficiencies. So why not do this right now, they ask? And they answer by suggesting that the following investigations first be undertaken:

1) Dose-response studies in persons with low vitamin B_{12} status due to food-cobalamin malabsorption, the most common cause of low cobalamin status in the elderly.

2) Evidence of benefit from randomized trials using low-dose vitamin B_{12} with clinical outcomes; current trial evidence, even from high-dose trials, is far from unequivocal.

3) Evidence of a lack of adverse effects in large-scale trials; thus far, studies have not been designed to assess such effects. Observational studies that have reported an association of B_{12} status or intake with an increased risk of cancer should not be ignored.

4) Cyanocobalamin is rather unstable and may form cobalamin analogues that interfere with normal cobalamin metabolism and transport.

5) Before fortification is introduced, a coherent plan should be developed to document changes in vitamin B_{12} status; to monitor the effects on NTD births, on cognition, and anemia in the elderly; and to assess the possible occurrence of untoward effects on the population.

6) While waiting for a decision on vitamin B_{12} fortification, authorities urgently need to consider how to manage the newly discovered large-scale problem of those with low vitamin B_{12} status and high folate status in countries that have fortified with folic acid.

All of this takes on added urgency in view of an important recent study in which an association was made between low vitamin B_{12} status and rate of brain volume loss/shrinkage in the elderly. This was a prospective study of 107 community-dwelling volunteers aged 61 to 87 without cognitive impairment at enrollment. The subjects were evaluated annually for five years by clinical examination, MRI scans and cognitive tests. The association observed remained significant after adjustment for age, sex, initial brain volume and several other relevant variables. Confidence in the result was boosted by the fact that this study measured markers of vitamin B_{12} status more sensitive than those used in previous studies, most of which merely measured total plasma vitamin B_{12}. The researchers hypothesized that vitamin B_{12} might help diminish inflammation in the brain and help preserve the integrity of brain myelin. Larger trials are needed to further confirm and expand these findings.

Neurologic symptoms of vitamin B_{12} deficiency can occur, contrary to what was previously believed, in the absence of predecessor hematologic abnormalities. Among neurologic abnormalities noted are those involving the spinal cord, peripheral nerves, optic nerves and cerebrum. Sensory disturbances, such as paresthesias in the extremities, are considerably more common than motor disturbances. Neuropathies and myelopathies can occur alone or in combination. Cognitive impairment and mood changes are more common than dementia, psychosis, paranoia and violent behavior. There are rare instances of visual impairment. Age-related hearing loss has been associated with B_{12} and folate deficiency in the elderly. Researchers stress the need for prompt treatment. These conditions, if left untreated, often become irreversible.

Those with mild deficiency usually suffer only from neuropathy and modest memory impairment. Some immuno-

logic deficits are also sometimes noted, but it is not known if these are caused by the deficiency. Supplemental vitamin B_{12} successfully reverses mild memory impairment and neuropathy in most elderly subjects deficient in this vitamin.

The Food and Nutrition Board has recommended that elderly people obtain 2.4 micrograms of vitamin B_{12} daily—from verifiable sources, e.g., either from eating fortified foods, such as cereals, that clearly identify the amount of vitamin B_{12} per serving and/or from vitamin B_{12} supplements. And some researchers, again noting the danger of irreversibility of neurologic symptoms that go untreated, have recently recommended regular periodic screening of the elderly for detection of vitamin B_{12} deficiency at an early stage.

A high prevalence of vitamin B_{12} deficiency has also been reported in those who have had gastric surgery. A recent study detected this deficiency in 31% of those who had undergone this type of surgery, compared with 2% of controls of similar age and race. Previous studies had noted an incidence of vitamin B_{12} deficiency of 1%-20% in gastric surgery patients, but the most recent study used more metabolic variables to detect the deficiency and tested an older patient sample. It also looked for the deficiency over a longer period of time. Median age of subjects in this study was 67 years.

These researchers found that vitamin B_{12} deficiency is often undetected in post-gastric surgery patients whose subsequent neurologic symptoms are often misdiagnosed. Most had not been advised, after surgery, to be monitored for vitamin B_{12} deficiency. These researchers stress the need for regular vitamin B_{12} screening in all gastric surgery patients, no matter how many years elapsed since the surgery. They point out that vitamin B_{12} deficiency may develop many years after surgery.

Vitamin B_{12} deficiencies have been reported in some chronically ill populations. Vitamin B_{12} has been found to be malabsorbed in some with HIV disease. There have also been reports of vitamin B_{12} deficiency in individuals with chronic fatigue of various etiologies. There are anecdotal reports that supplemental vitamin B_{12} is helpful in these disorders. Controlled trials are lacking.

Two placebo-controlled trials have shown that a combination of vitamin B_{12} and folic acid inhibited a precursor of bronchial squamous cell cancer of the lung in humans. In one of these studies, supplementation with 10 milligrams of folic acid daily, combined with 500 micrograms of vitamin B_{12} daily, for four months, produced a significant reduction in the number of subjects, all heavy smokers, who exhibited the abnormal bronchial cells said to be cancer precursors.

Many researchers have noted that diminished vitamin B_{12} status is strongly associated with hyperhomocysteinemia, a significant risk factor for cardiovascular disease. Two researchers have noted that, "although folate deficiency is a far more common cause of elevated homocysteine levels than are vitamin B_{12} and vitamin B_6 deficiencies, an elevated homocysteine value in an older person should not be considered due to folate deficiency alone. Because elderly people may have elevated homocysteine levels due to vitamin B_{12} deficiency, lowering serum total homocysteine levels to reduce the high incidence of vascular disease among the elderly by supplying adequate amounts of all three vitamins may become an important public health issue."

Recently, diminished vitamin B_{12} status has been identified as an additional nutritional risk factor for breast cancer among post-menopausal women. This preliminary finding needs follow-up before its significance, if any, can be assessed.

Claims that vitamin B_{12} can enhance exercise performance and that it is an "energizer" have not been tested and are based upon anecdotal accounts.

There is evidence that some who are on strict vegetarian or macrobiotic diets may need supplemental vitamin B_{12}. Children and the elderly who are on these diets may, in particular, have need of this supplementation. Some have claimed that miso, tamari, tempeh and other soy products can provide adequate B_{12} in the absence of meats and dairy products. This has not been demonstrated. Nor has the claim that adequate B_{12} can be obtained from spirulina, sea weeds and other sea vegetables. Even unpasteurized miso, claimed to be an excellent source of B_{12}, appears to have very little to none of the vitamin. Nor can vegetarians get adequate B_{12} from brewer's yeast, grains, cereals or mushrooms. Some sea vegetables are said to contain significant amounts of vitamin B_{12}, but accumulating evidence suggests that, instead, these foods contain vitamin B_{12} analogues (pseudovitamin B_{12}) that do not confer the functions and protection of vitamin B_{12} itself.

Again, vitamin B_{12} supplementation is highly advised for vegetarians, especially children who are vegetarians. Vegetarians whose diets allow for the regular use of eggs and dairy products can generally obtain enough vitamin B_{12} from their diets. Vegetarians consume certain foods (garlic, onions) that contain certain substances (e.g., inulins) which stimulate the growth of certain bacteria (e.g., *lactobacillus*) in the colon. These bacteria produce B_{12} and may supply some of the vitamin to the body. However, this needs to be proven.

Finally, there is evidence that vitamin B_{12} can protect some from allergy to the sulfites that are added to some foods and wines. In one study, 2,000 micrograms of sublingual vitamin B_{12} significantly prevented reactions to sulfites in 17 of 18 sulfite-sensitive subjects challenged with sulfites. Subsequent placebo-controlled trials confirmed this protective effect.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Vitamin B_{12} (cyanocobalamin, hydroxocobalamin, methylcobalamin) is contraindicated in those hypersensitive to any component of a vitamin B_{12}-containing product.

PRECAUTIONS

The use of vitamin B_{12} to treat vitamin B_{12} deficiency or to treat any medical condition requires medical supervision.

Cyanocobalamin should not be used in those with Leber's optic atrophy. This is a congenital disorder associated with chronic cyanide intoxication (e.g., from tobacco smoke). Decreased levels of B_{12} have been associated with reduced ability to detoxify the cyanide in exposed individuals and cyanocobalamin may increase the risk of irreversible neurological damage from optic atrophy in those affected with the disorder. Hydroxocobalamin can aid in the detoxification of cyanide. This form of B_{12} is an acceptable form for B_{12} supplementation in those with this disorder.

A typical dose of B_{12} (cyanocobalamin) in nutritional supplements used by pregnant women and nursing mothers is 12 micrograms daily. Pregnant women and nursing mothers should only use doses higher than this if recommended by their physicians.

Administration of doses of vitamin B_{12} greater than 10 micrograms daily may produce a hematological response in those with anemia secondary to folate deficiency.

ADVERSE REACTIONS

Oral vitamin B_{12} is well tolerated even at high doses. There are occasional reports of hypersensitivity reactions (urticaria, rash, pruritus) in those receiving parenteral B_{12}. Those who have experienced hypersensitivity reactions from use of parenteral B_{12} may experience similar reactions from oral B_{12}, although there are very few reports of this occurring.

INTERACTIONS

DRUGS

Antibiotics: The use of antibiotics may alter the intestinal microflora and may decrease the possible contribution of B_{12} by certain inhabitants of the microflora (e.g., *Lactobacillus* species) to the body's requirement for the vitamin. This may particularly be a problem for vegetarians. Garlic, onions, leeks, bananas, asparagus and artichokes, among other vegetables and fruits, contain inulins which promote the growth of certain colonic bacteria, including *Lactobacillus* species (see Inulins).

Cholestyramine: Cholestyramine may decrease the enterohepatic reabsorption of B_{12}.

Colchicine: Colchicine may cause decreased absorption of B_{12}.

Colestipol: Colestipol may decrease the enterohepatic reabsorption of B_{12}.

H_2 blockers (cimetidine, famotidine, nizatidine, ranitidine): Chronic use of H_2 blockers may result in decreased absorption of vitamin B_{12} naturally found in food sources. They are unlikely to affect the absorption of supplemental B_{12}.

Metformin: Metformin may decrease the absorption of vitamin B_{12}. This possible effect may be reversed with oral calcium supplementation.

Nitrous oxide: Inhalation of the anesthetic agent nitrous oxide (not to be confused with nitric oxide) can produce a functional vitamin B_{12} deficiency. Nitrous oxide forms a complex with cobalt in methylcobalamin, the cofactor for methionine synthase, resulting in inactivation of the enzyme.

Para-aminosalicylic acid: Chronic use of the anti-tuberculosis drug may decrease the absorption of B_{12}.

Potassium chloride: It has been reported that potassium chloride may decrease the absorption of dietary B_{12} in some.

Proton pump inhibitors (lansoprazole, omeprazole, pantoprazole, rabeprazole): Chronic use of proton pump inhibitors may result in decreased absorption of vitamin B_{12} naturally found in food sources. They are unlikely to affect the absorption of supplemental B_{12}.

NUTRITIONAL SUPPLEMENTS

Calcium: Calcium supplementation may reverse the possible metformin-induced decrease of B_{12} absorption.

Folate: Folic acid may work synergistically with vitamin B_{12} in lowering homocysteine levels.

Vitamin B_6: Vitamin B_6 may work synergistically with vitamin B_{12} and folate in lowering homocysteine levels.

Vitamin C: Low serum B_{12} levels reported in those receiving large doses of vitamin C were artifacts of the effect of ascorbate on the radioisotope assay for B_{12}. There are no known interactions between vitamin C and vitamin B_{12}.

OVERDOSAGE

There are no reports of vitamin B_{12} overdosage in the literature.

DOSAGE AND ADMINISTRATION

The principal form of B_{12} used in nutritional supplements is cyanocobalamin. Methylcobalamin is also available for nutritional supplementation. Hydroxocobalamin is presently only available for parenteral use.

Cyanocobalamin is available as a single ingredient product and in multivitamin, multivitamin/multimineral and B complex products. Lozenges of cyanocobalamin and methylcobalamin are also available. Prenatal and postnatal vitamin/mineral formulas typically deliver a dose of 12 micrograms of B_{12} daily. A general range of B_{12} dosage is 3 to 30 micrograms daily. Some use much higher doses. Absorption of naturally occurring B_{12} decreases with age. Because of this, the Food and Nutrition Board advises that those older than 50 years should consume foods fortified with B_{12} or take a vitamin B_{12}-containing nutritional supplement in order to meet the RDA (2.4 micrograms daily).

Those with B_{12} deficiency may be managed with high doses of oral B_{12}. However, this requires prescription and management by a physician.

The Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences has recommended the following Dietary Reference Intakes (RDI) for vitamin B_{12}:

Infants	Adequate Intakes (AI)
0 through 6 months	0.4 micrograms/day ~ 0.05 micrograms/Kg
7 through 12 months	0.5 micrograms/day ~ 0.05 micrograms/Kg
Children	**Recommended Dietary Allowance (RDA)**
1 through 3 years	0.9 micrograms/day
4 through 8 years	1.2 micrograms/day
Boys	
9 through 13 years	1.8 micrograms/day
14 through 18 years	2.4 micrograms/day
Girls	
9 through 13 years	1.8 micrograms/day
14 through 18 years	2.4 micrograms/day
Men	
19 years and older	2.4 micrograms/day
Women	
19 years and older	2.4 micrograms/day
Pregnancy	
14 through 50 years	2.6 micrograms/day
Lactation	
14 through 50 years	2.8 micrograms/day

The DV (Daily Value) for vitamin B_{12} (cobalamin), which is used for determining the percentage of nutrient daily values on nutritional supplement and food labels, is 6 micrograms. This is based on the U.S. RDA for vitamin B_6.

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Vitamin C

DESCRIPTION

The term vitamin C applies to substances that possess antiscorbutic activity and includes two compounds and their salts: L-ascorbic acid, commonly called ascorbic acid, and L-dehydroascorbic acid. Ascorbic acid is the major dietary form of vitamin C. The terms vitamin C, ascorbic acid, L-ascorbic acid, L-ascorbate and ascorbate are commonly used interchangeably.

Vitamin C is a hexose derivative, similar in structure to the six-carbon sugar glucose. It is an essential nutrient for humans, and, as pointed out by Linus Pauling in 1970, "differs from other nutrients in that it is required in the diet by only a few species of animals—man, other primates, the guinea pig, an Indian fruit-eating bat, and the red-vented barbul and some related species of Passeriform birds." It is also an essential nutrient for Coho salmon, rainbow trout, carp and some insects. Most other animals, all higher plant species and probably all algal classes can synthesize vitamin C from glucose or other sugars. Molecules similar to ascorbic acid are made by some fungi but not by bacteria. All vitamin C requiring animals lack the enzyme L-gulano-gamma-lactone oxidase, the final step in the synthesis of ascorbic acid from glucose. Plants produce large amounts of ascorbic acid to facilitate resistance to the oxidative stresses associated with the myriad biotic and abiotic challenges inherent to photosynthesis.

The major deficiency syndrome of vitamin C is scurvy. Symptoms of scurvy include inflamed and bleeding gums, petechiae, ecchymosis, follicular hyperkeratosis, coiled hairs, perifollicular hemorrhages, impaired wound healing, dry eyes and mouth (Sjögren's syndrome), arthralgia, joint effusions, muscle weakness, myalgia, fatigue, depression, frequent infections, anemia, anorexia, diarrhea, and pulmonary and kidney problems that can lead to coma and death. All systems of the body are affected by scurvy.

The antiscorbutic factor was isolated from the ox adrenal cortex in 1927 by the Hungarian biochemist and Nobel laureate Albert Szent-Györgyi and his colleagues, although at the time Szent-Györgyi didn't know that it was the antiscorbutic factor. In fact, his interest then was not in vitamins at all but in biological oxidation and reduction, and he was looking for reducing substances in extracts of the adrenal cortex. What was later to be known as ascorbic acid, Szent-Györgyi called "C XII" since it was the 12th substance prepared and examined in his work on tissue oxidation and the function of the adrenal cortex. He later discovered that C XII was indeed vitamin C, the antiscorbutic factor, that its empirical formula was $C_6H_8O_6$ and that the molecule was a carbohydrate, most likely a sugar derivative. He submitted a paper on his discovery, which he named Ignose (from "ignosco"—"I don't know" in Latin—and "-ose" to indicate that it was a member of the sugar family). However, the editor of the journal rejected that name and also the next one that Szent-Györgyi came up with, "Godnose." The editor suggested "hexuronic acid" to indicate that it had six carbons and was a sugar acid similar to glucuronic acid. Szent-Györgyi gave in and accepted that name, which shortly was to change to ascorbic acid. Szent-Györgyi actually didn't know the exact structure of ascorbic acid, which explains Ignose and Godnose. It was the chemist and also Nobel laureate Walter Haworth who actually deciphered the structure. Szent-Györgyi found a rich source of ascorbic acid in the fruit of the Hungarian red pepper or paprika (*Capsicum annuum*). He also found some other interesting reducing agents in paprika. He called these substances vitamin P. They were the first flavonoids identified. In 1932, the American biochemist Glen King and his colleagues isolated ascorbic acid from lemon juice, which is where the vitamin C story first began. Well, actually lime juice, but close enough.

Many of the symptoms of scurvy, particularly those having to do with connective tissue, can be explained by the known biochemical roles of vitamin C, particularly its role as a cofactor for prolyl and lysyl hydroxylase, enzymes important in the formation of collagen. Collagen synthesized in the absence of ascorbic acid—as occurs in scurvy—cannot properly form fibers, resulting in blood-vessel fragility, among other defects. In the prolyl and lysyl hydroxylase reactions, as well as in most of the biochemical reactions ascorbic acid participates in, it acts as a reducing agent. In these reactions, the vitamin reduces ferric and cupric ions to their ferrous and cuprous states, forms which are required for the reactions to proceed.