



**Aunt Cathy**

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## **Aunt Cathy's Guide to Nutrition: A Vitamin B12 Update**

### **Full Reference Version**

Vitamin B12 is needed in only tiny amounts, and unlike most B vitamins, it is stored well in the body. Most Americans eat foods that provide lots of it. So there shouldn't be any problem with vitamin B12, right? This is a Trick Question of course; if there were no problem I would not be here talking about it! ☺

Most references for the information provided here are included at the end. A few newer ones are sprinkled around in the text. As always, this handout is not intended to take the place of your physician or health care provider. It is simply a summary of the most recent information available in the scientific literature on this topic as of the date shown.

### **What does B12 do?**

1. B12 is involved in making important chemical messengers and myelin in the brain and nervous system, so some of the major symptoms of deficiency are neurologic problems.
2. B12 is involved in the making DNA, the genetic center of every cell in the body. It is especially important during periods of growth (pregnancy, infancy and childhood), and in tissues that continually make a lot of new cells (red blood cells and the armies of cells in the immune system.)

### **What happens if B12 is too low?**

Besides serious nerve damage and mental confusion, B12 deficiency damages the retina of the eye, and may play a role in conditions such as heart disease, stroke, Alzheimer's disease, incontinence and loss of hearing. When deficiency is severe, people can have unusually high heart rates and

have trouble breathing. Vitamin B12 deficiency causes changes in testicular tissues in men, and it may be related to increased risk of breast cancer in older women.

During pregnancy, inadequate B12 causes birth defects such as neural tube defects and brain damage. A new study suggests that underlying vitamin B12 deficiency may be involved in the development of HELLP Syndrome, a serious complication of pregnancy. [HELLP syndrome-like by vitamin B12 Deficiency: Report of seven cases. J Gynecol Obstet Biol Reprod (Paris). 2009 Mar 20]

## **What foods have B12?**

The only natural food sources are animal products like meat, poultry, fish, milk, cheese and eggs. Other foods may have it added.

## **Who is at risk of low B12 status?**

### **1. People with inadequate B12 in their diet.**

**Strict Vegans** (people who use no animal products) **and their breast-fed babies** are at high risk unless they take a B12 supplement. **Some people just eat a really poor diet** that happens to be very low in both meats and dairy foods.

### **2. Some people do not absorb B12 well in spite of an adequate diet.**

#### **Stomach problems that may decrease B12 absorption:**

Gastrectomy (stomach removal);

Gastric surgery for weight loss

[Anemia after bariatric surgery: more than just iron deficiency. Nutr Clin Pract. 2009]

Low stomach acid production or atopic gastritis (both common problems among the elderly);

Infection with H. Pylori, a bacteria that causes ulcers and gastritis;

Genetic factors causing low levels of "Intrinsic Factor," a B12 carrier made in the stomach.

#### **Conditions that affect the part of the small intestine where it joins the large intestine (called the "terminal ileum"):**

Surgical removal of that part of the intestine;  
Crohn's disease (inflammatory bowel disease) or celiac disease;  
Overgrowth of the intestine surface by bacteria or parasites such as giardia. This is especially common among adults older than 70 who have chronic diarrhea, loss of appetite, or nausea.

[Vitamin B12 status, methylmalonic acidemia, and bacterial overgrowth in short bowel syndrome. J Pediatr Gastroenterol Nutr. 2009 Apr;48(4):495-7.]

### **Some medications interfere with absorption of B12 from food.**

Medications probably account for the surprisingly greater number of younger adults now being found to be deficient in B12. Drugs that block stomach acid production (like **Tagamet, Zantac and especially “proton pump inhibitors” like Prilosec, Nexium, Previcid and Protonics**) and the diabetes drug **Metformin (Glucophage)** all interfere with B12 absorption. Additionally, people with low vitamin B12 status are at great risk if **nitrous oxide anesthesia** is used.

### **People with autoimmune disorders such as insulin-dependent diabetes, celiac disease, multiple sclerosis, and certain thyroid disorders have a higher risk of deficiency for several reasons.**

Sometimes it is related to nutrient malabsorption related to intestinal damage from poorly controlled celiac disease. However, as another autoimmune disorder, the severe vitamin B12 deficiency called pernicious anemia is also more common in this population. In some people with celiac disease, neurologic symptoms are not uncommon ... it is important to monitor their B12 levels carefully.

**In insulin dependent diabetes or multiple sclerosis, however, neurologic symptoms of pernicious anemia are often missed because they are written off as likely due to neurologic damage from those overriding conditions.** An adult friend of mine with type 1 diabetes experienced extremely debilitating neurologic symptoms because of having developed the autoimmune disease pernicious anemia. She could no longer walk and the pain was severe. Her symptoms were ascribed to complications of diabetes, and I am sorry to report that it took quite a lot of pressure and several months

to get the health care professionals involved in her care to check her vitamin B12 level.

She has improved greatly on vitamin B12 shots since then, but the painful neurologic damage will never be completely gone. Pernicious anemia has been documented in adolescents with diabetes, celiac disease, and autoimmune thyroid disorders as well as in adults, especially among those already identified as having two or more autoimmune diseases. [

Pernicious anemia in an adolescent with type 1 diabetes mellitus. Arch Pediatr Apr;16(4):357-9]

Interestingly, parenteral vitamin B12 does look like it can be helpful in diabetic neuropathy, whether related to underlying pernicious anemia or not.

[Vitamin B12 may be more effective than nortriptyline in improving painful diabetic neuropathy. Int. J. Food Sci 2009 Feb 12:1-6]

## **How is B12 deficiency recognized?**

Most commonly it is recognized when a blood test called a CBC shows red blood cells that are very large ("macrocytic anemia.") Unfortunately, this is a very **late-appearing symptom** and some nerve damage will have already happened by the time the problem is recognized. **It takes up to three years for symptoms of deficiency to develop**, so people often fail to associate the symptoms with a change in diet or health (such as having had stomach surgery, starting to use a certain medication, or deciding to follow a vegan diet.)

Some researchers estimate that as many as **30% of elderly people have unrecognized B12 deficiency**, often due to changes in the stomach and intestine caused by aging. This can contribute to symptoms such as confusion and other mental changes; correcting B12 inadequacy often results in great improvement.

Doctors can check **B12 levels in the blood**, and there are other markers called **homocysteine** and **methylmalonic acid (MMA)**. This testing is not commonly done unless symptoms or risk factors suggest that there is a problem. However, it is impractical, expensive and unnecessary to do these tests regularly on everyone.

## **What should be done?**

Quite a lot can be done to decrease the likelihood of B12 deficiency ever developing. Why risk possible inadequacy? **Assuring adequacy** is by far more cost-effective, health-protective and safe than waiting to act until symptoms of inadequacy become apparent.

- 1. An inexpensive generic standard multivitamin with minerals is likely a very good investment for most people.** These provide the adult RDA of 2 mcg of well-absorbed B12. Products designed for older adults ("**Silver**"-type **multivitamins**) often have 25 mcg. Some have quite a lot more, as do some "B-100 complex" supplements. **Some researches now recommend >50 mcg/day. B12 is a very safe vitamin and overdose is extremely unlikely.** For some of the conditions (such as **low stomach acid**), simply taking a generous amount of vitamin B12 in a supplement form can solve the problem.
- 2. For other conditions (such as surgical removal of the stomach or part of the intestine or autoimmune-related pernicious anemia), prescription B12 shots are often needed** to assure that there is enough in the body. New techniques include nasal inhalers, sub-lingual (under the tongue) versions, or extremely high oral doses of B12. As always, it is extremely important to monitor the effectiveness of any of these methods.

### **Summary:**

**Vitamin B12 deficiency is not uncommon (although it is often unrecognized) and it is very dangerous.**

**Certain diet patterns or health conditions increase the risk of unrecognized B12 deficiency.** People with any of the risk factors described above should be sure to ask their doctors about this issue. Sharing this column with the doctor may be helpful.

**The problem of unrecognized vitamin B12 deficiency is just one of the many reasons why it is regarded as "prudent" for all adults to take a daily multivitamin.** (Journal of the American Medical Association, June 2002.)

(Some references, abstracts and comments follow.)

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# Some references for vitamin B12 and the elderly, proton pump inhibitors and/or metformin

Jensen RT. **Consequences of long-term proton pump blockade: insights from studies of patients with gastrinomas.** *Basic Clin Pharmacol Toxicol.* 2006 Jan;98(1):4-19. Proton pump inhibitors are being increasingly used and for longer periods of time, especially in patients with gastroesophageal reflux disease. Each of these trends has led to numerous studies and reviews of the potential risk-benefit ratio of the long-term use of proton pump inhibitors. Both long-term effects of hypergastrinaemia due to the profound acid suppression caused by proton pump inhibitors as well as the effects of hypo-/achlorhydria per se have been raised and studied. Potential areas of concern that have been raised in the long-term use of proton pump inhibitors, which could alter this risk-benefit ratio include: gastric carcinoid formation; the development of rebound acid hypersecretion when proton pump inhibitor treatment is stopped; the development of tolerance; increased oxyntic gastritis in *H. pylori* patients and the possibility of increasing the risk of gastric cancer; the possible stimulation of growth of non-gastric tumours due to hypergastrinaemia; and the possible effect of the hypo/achlorhydria on nutrient absorption, particularly iron and vitamin B12. **Because few patients with idiopathic gastro-oesophageal reflux disease/peptic ulcer disease have been treated long-term (i.e., >10 years), there is little known to address the above areas of potential concern. Most patients with gastrinomas with Zollinger-Ellison syndrome have life-long hypergastrinaemia, require continuous proton pump inhibitors treatment and a number of studies report results of >5-10 years of treatment and follow-up. Therefore, an analysis of Zollinger-Ellison syndrome patients can provide important insights into some of the safety concerns raised above. In this paper, results from studies of Zollinger-Ellison syndrome patients and other recent studies dealing with the safety concerns above, are briefly reviewed.**

Liu KW, Dai LK, Jean W. **Metformin-related vitamin B12 deficiency.** *Age Ageing.* 2006 Mar;35(2):200-1. Metformin is an invaluable hypoglycaemic agent. We report two cases who had symptomatic vitamin B12 deficiency related to metformin use; the mechanisms are discussed. The clinician must be aware of the possibility of metformin-associated B12 deficiency in users who suffer cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia.

Kilicdag EB, Bagis T, Tarim E. **Administration of B-group vitamins reduces circulating homocysteine in polycystic ovarian syndrome patients treated with metformin: a randomized trial.** *Hum Reprod.* 2005 Jun;20(6):1521-8. Background: The aim of the current study was to assess the effects of B-group vitamins and folic acid administration on serum levels of homocysteine (Hcy) in patients with polycystic ovarian syndrome (PCOS) on short-term metformin treatment. Methods: Patients were randomly assigned to one of three treatment groups. Group 1 patients (n = 20) received metformin (850 mg twice daily); group 2 patients (n = 20) received metformin (850 mg twice daily) and B-group vitamins (vitamin B1, 250 mg; vitamin B6, 250 mg; vitamin B12, 1000 microg twice daily); and group 3 patients (n = 20) received metformin (850 mg twice daily) and folic acid (174 microg twice daily). In all groups, lipid profiles and plasma total Hcy, vitamin B12, folic acid and glucose levels were recorded at baseline and at 3 months. Results: A 26.5% increase in Hcy levels was seen after 12 weeks of metformin therapy, while 21.17 and 8.33% decreases in Hcy levels were detected when B-group vitamins or folic acid plus metformin were given respectively. There were no statistically significant differences recorded in insulin sensitivity using homeostasis model assessment in the three groups. Conclusion: These findings suggest that B-group vitamins and folic acid administration counteract the Hcy-increasing effect seen with metformin therapy.

Elphick DA, Chew TS, Higham SE. **Small bowel bacterial overgrowth in symptomatic older people: can it be diagnosed earlier?** *Gerontology.* 2005 Nov-Dec;51(6):396-401. Background/Objectives In older people, small bowel bacterial overgrowth syndrome may be a common, but under-diagnosed, cause of diarrhoea and nutrient malabsorption. We aim to determine which clinical features and baseline laboratory investigations indicate a high likelihood of small bowel bacterial overgrowth as defined by a positive glucose breath test. Methods: A retrospective analysis of records for all patients referred for glucose breath test over a 6-year period to a teaching hospital. Results: Out of 197 referrals, 168 patient records were located and analysed (62 male, 106 female; median age 65). Patient characteristics predictive of a positive glucose breath test were: increasing age (p < 0.01), low serum vitamin B12 (p = 0.02), low serum albumin (p = 0.03), previous partial gastrectomy (p < 0.01), previous right hemi-colectomy (p < 0.01), presence of small bowel diverticulae (p = 0.01) and concurrent use of a proton pump inhibitor (p < 0.01). 52.5% (n = 21/40) of patients studied who were over 75 years old versus 21.8% (n = 28/128) of those under 75 years old had a positive glucose breath test (p < 0.01). The median time to diagnosis, from first hospital visit to positive glucose breath test, was 39 weeks. Conclusions: There is often a significant delay in diagnosis of small bowel bacterial overgrowth. We suggest that this diagnosis should be considered earlier in the investigative algorithm in older patients with indicative symptoms and a **predisposing factor (including previous partial gastrectomy, previous right hemi-colectomy, small bowel diverticulae or use of a proton pump inhibitor) or concurring laboratory indices (low vitamin B12 or albumin).**

Wiersinga WJ, de Rooij SE, Huijmans JG. **Diagnosis of vitamin B12 deficiency revised** *Ned Tijdschr Geneesk.* 2005 Dec 10;149(50):2789-94. **Vitamin B12 (cobalamin) deficiency is a common disorder with potential irreversible haematological and neurological consequences. Currently used diagnostic tests such as the evaluation of serum vitamin B12 and the Schilling test are insufficient,** e.g. the positive predictive value of a low serum vitamin B12 level for actual vitamin B12 deficiency (i.e. tissue deficiency) is low. Insufficient availability of vitamin B12 will lead to the accumulation of methylmalonic acid and homocysteine in the body. Nearly all patients with vitamin B12 deficiency also have substantially increased levels of methylmalonic acid and homocysteine. New tests of serum methylmalonic acid and homocysteine are highly sensitive for vitamin B12 deficiency and may obviate the need for the somewhat cumbersome Schilling test.

Wolters M, Strohle A, Hahn A. **Cobalamin: a critical vitamin in the elderly.** *Prev Med.* 2004 Dec;39(6):1256-66. Vitamin B(12) deficiency is a common problem in elderly subjects. If a serum cobalamin level of about 150 pmol/L (200 pg/mL) is considered normal, 10-15% of the elderly are deficient. Today, however, a threshold of 220-258 pmol/L (300-350 pg/mL) is recognized as desirable in the elderly, or else sensitive markers like the blood concentration of homocysteine or methylmalonic acid (MMA) are used. Then the prevalence of cobalamin deficiency rises to up to 43%. In the elderly, this high prevalence of poor cobalamin status is predominantly caused by atrophic gastritis type B. Atrophic gastritis results in declining gastric acid and pepsinogen secretion, and hence decreasing intestinal absorption of the cobalamin protein complexes from food. About 20-50% of the elderly are affected. Furthermore, the reduced acid secretion leads to an alkalization of the small intestine, which may result in bacterial overgrowth and thus to a further decrease of the bioavailability of the vitamin. In addition, some drugs such as proton pump inhibitors or H2 receptor antagonists inhibit the intestinal absorption of vitamin B(12). An already moderately reduced vitamin B(12) level is associated with vascular disease and neurocognitive disorders such as depression and impaired cognitive performance. Furthermore, a poor vitamin B(12) status is assumed to be involved in the development and progression of dementia (e.g., Alzheimer's dementia). This is especially observable if the folic acid status is reduced as well. Due to the insecure supply, the cobalamin status of elderly persons (>=60 years) should be regularly controlled and a general supplementation with vitamin B(12) (>50 microg/day) should be considered.

**Pongchaidecha M, Srikusalanukul V, Chattananon A. Effect of metformin on plasma homocysteine, vitamin B12 and folic acid: a cross-sectional study in patients with type 2 diabetes mellitus.** *J Med Assoc Thai.*

2004 Jul;87(7):780-7. .OBJECTIVE: To determine the effect of metformin on the levels of plasma homocysteine (Hcy), serum vitamin B12 and folic acid in patients with type 2 diabetes mellitus and the relationship between cumulative metformin exposure and levels of plasma homocysteine (Hcy). MATERIAL AND METHOD: The cross sectional study was conducted to assess the effect of metformin treatment on plasma homocysteine (Hcy), serum vitamin B12 and folic acid in 152 type 2 diabetic out-patients aged between 35-65 years old at the Diabetes Clinic of The Makaruk Hospital, Kanchanaburi, Thailand Among those, 88 and 64 patients were categorised to the metformin and non-metformin group according to their records of receiving metformin treatment for a period of a minimal 6 consecutive months before the study. Fasting blood was drawn from each patient and analysed for plasma homocysteine using the Fluorescence Polarization Immunoassay (FPIA) method (IMX Analyzer), and serum vitamin B12 and folic acid using the radioimmunoassay method RESULTS: The plasma Hcy levels showed no significant difference (p = 0.544) among patients in the metformin group compared with those in the non-metformin group (10.6+/-5.8 mol/L vs 10.4+/-4.0 mol/L). There was a significant difference (p = 0.011) in the levels of serum vitamin B12 among patients in the metformin group and among those in the non-metformin group (318.0+/-192.2 pg/mL vs 434.3+/-300.7 pg/mL). However, there was no significant difference (p = 0.090) in serum folic acid levels between patients in the metformin and those in the non-metformin group (8.8+/-5.1 ng/mL vs 7.7+/-3.8 ng/mL). The plasma Hcy levels showed a significant correlation with the duration of metformin treatment (p = 0.014) and the amount of metformin received (p = 0.015) with the Spearman correlation coefficient of 0.260 and 0.258 respectively. CONCLUSION: Even though the direct effect of metformin treatment on the plasma Hcy could not be concluded from the present study, it was found that there was a significant depletion of level of serum vitamin B12 among patients who had been on long-term metformin treatment. Therefore, vitamin B12 supplement is suggested for diabetic patients who are receiving metformin medication.

Buvat DR. **Use of metformin is a cause of vitamin B12 deficiency.** *Am Fam Physician.* 2004 Jan 15;69(2):264; 264, 266. No abstract available.

**Valuck RJ, Ruscini JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults.** *J Clin Epidemiol.* 2004 Apr;57(4):422-8

Objective: Acid-suppressant drugs are commonly prescribed for elderly patients, a population in which vitamin B(12) deficiency is a common disorder. The purpose of this study was to examine the possible association between use of prescription histamine H-2 receptor antagonists (H2RA) or proton pump inhibitors (PPI) and vitamin B(12) deficiency in older adults. Study Design and Setting: This was a case-control study in a University-based geriatric primary care setting. Among patients aged 65 years or older with documented serum vitamin B(12) studies between 1990 and 1997, 53 vitamin B(12)-deficient cases were compared with 212 controls for past or current use of prescription H2RA/PPI according to information in subjects' medical records. Results: Controlling for age, gender, multivitamin use, and Helicobacter pylori infection, chronic (#10878;12 months) current use of H2RA/PPI was associated with a significantly increased risk of vitamin B(12) deficiency (OR 4.45; 95% CI 1.47-13.34). No association was found between past or short-term current use of H2RA/PPI and vitamin B(12) deficiency. Conclusion: These findings support an association between chronic use of H2RA/PPI by older adults and development of vitamin B(12) deficiency. Additional studies are needed to confirm these findings.

**Force RW, Meeker AD, Cady PS. Ambulatory care increased vitamin B12 requirement associated with chronic acid suppression therapy.** *Ann Pharmacother.* 2003 Apr;37(4):490-3.

Background: Assimilation of vitamin B(12) from dietary sources requires gastric acid. By decreasing acid production, the proton pump inhibitors (PPIs) and histamine(2) (H(2))-blockers may reduce vitamin B(12) absorption. Objective: To determine whether chronic acid suppression therapy is associated with the initiation of vitamin B(12) supplementation, we conducted a retrospective case-control study using a state-wide Medicaid population. Methods: Case patients were identified as those who initiated vitamin B(12) supplementation during the study period. Four control patients were age- and gender-matched to each case. Patients (n = 109 844) with a paid claim between September 27, 1995, and September 27, 1997, were eligible for inclusion. Chronic acid suppression therapy was defined as treatment with H(2)-blockers or PPIs for >=10 of the 12 months prior to the first vitamin B(12) injection. Comparisons were made between the case and control groups regarding exposure to chronic acid suppression therapy. Results: One hundred twenty-five cases were matched to 500 controls. Twenty-three patients

(18.4%) had been exposed to chronic acid suppression therapy compared with 55 (11.0%) of the control group ( $p = 0.025$ ; OR 1.82; 95% CI 1.08 to 3.09). Conclusions: **Initiation of vitamin B(12) supplementation was associated with chronic gastric acid suppression therapy.**

**Wulfefe MG, Kooy A, Leher P. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial.**

*J Intern Med.* **2003** Nov;254(5):455-63. Objective: Metformin is a key treatment option in type 2 diabetes. However, metformin may decrease vitamin B12 levels and increase levels of homocysteine, a cardiovascular risk factor. We investigated whether 16 weeks of treatment with metformin affects serum concentrations of homocysteine, folate and vitamin B12 in subjects with type 2 diabetes treated with insulin. Design: Placebo-controlled, randomized trial. Measurements: at baseline and 16 weeks later. Setting: This trial was conducted in the outpatient clinics of three general hospitals in The Netherlands. Subjects: A total of 745 patients with type 2 diabetes, treated with insulin and not known with a contraindication for the use of metformin, were approached; 390 gave informed consent and entered the study. Thirty-seven subjects dropped out (12 placebo and 25 metformin users). Intervention: Addition of metformin or placebo to insulin therapy. Primary Outcome Parameters: Serum homocysteine, folate, vitamin B12, indices of glycaemic control and body weight. Results: Amongst those who completed 16 weeks of treatment, metformin use, as compared with placebo, was associated with an increase in homocysteine of 4% (0.2 to 8;  $P=0.039$ ) and with decreases in folate [-7% (-1.4 to -13);  $P=0.024$ ] and vitamin B12 [-14% (-4.2 to -24);  $P<0.0001$ ]. In addition, the increase in homocysteine could be explained by the decreases in folate and vitamin B12. Conclusion: In patients with type 2 diabetes, 16 weeks of treatment with metformin reduces levels of folate and vitamin B12, which results in a modest increase in homocysteine. The clinical significance of these findings remains to be investigated.

**Schubert ML. Gastric secretion.** *Curr Opin Gastroenterol.* **2003** Nov;19(6):519-25. Purpose of review: **Gastric acid facilitates the digestion of protein and the absorption of iron, calcium, and vitamin B12.** It also protects against bacterial overgrowth and enteric infection, including prion disease. When homeostatic mechanisms malfunction, the volume and concentration of acid may overwhelm mucosal defense mechanisms, leading to duodenal ulcer, gastric ulcer, and gastroesophageal reflux disease. This article reviews recent knowledge contributing to understanding of the regulation of gastric acid secretion at the central, peripheral, and intra-cellular levels. Recent Findings: The vagus nerve contains afferent fibers that transmit sensory information from the stomach to the nucleus of the solitary tract. Input from the nucleus of the solitary tract is relayed to vagal efferent neurons that originate from two brain stem nuclei: the nucleus ambiguus and the dorsal motor nucleus of the vagus. The latter is also influenced by thyrotropin-releasing hormone neurons that act centrally to stimulate acid secretion. The main peripheral stimulants of acid secretion are the hormone gastrin and the paracrine amine histamine. Gastrin stimulates acid secretion directly and, more importantly, indirectly by releasing histamine from fundic entero-chromaffin-like cells. Gastrin also exerts trophic effects on various tissues, including the gastric and intestinal mucosa. The main inhibitor of acid secretion is somatostatin. Somatostatin, acting via ssTR2 receptors, exerts a tonic paracrine inhibitory influence on the secretion of gastrin, histamine, and acid secretion. Calcitonin gene-related peptide, adrenomedullin, amylin, atrial natriuretic peptide, and pituitary adenylate cyclase-activating polypeptide all stimulate somatostatin secretion and thus inhibit acid secretion. HK-ATPase, the proton pump of the parietal cell, is stored within cytoplasmic tubulovesicles during the resting state, but during stimulation, it is shuttled to the canalicular membrane by a poorly understood mechanism that probably involves soluble N-ethylmaleimid- sensitive factor attachment protein receptor proteins. The proton pump inhibitor, pantoprazole, is unique in that it binds cysteine 822, located deep within the membrane domain of the alpha-subunit. The difficulty that reducing agents, such as glutathione, have in reaching cysteine 822 may be responsible for the longer half-time for acid recovery observed with pantoprazole. Hypergastrin-emia, induced by proton pump inhibitors, enhances expression of cyclooxygenase-2 and hence prostaglandins within parietal cells, a feedback pathway that may protect the stomach against acid-induced damage. Summary: In the past year, significant advances have been made in understanding of the regulation of gastric acid secretion. Ultimately, these advances should lead to improved therapies to prevent and treat acid-related disorders. Gastric acid secretion must be precisely controlled at a variety of levels to prevent disease caused by hyperchlorhydria and hypochlorhydria. The mechanisms include neural (central and peripheral), hormonal, paracrine, and intracellular pathways that operate in concert to switch acid secretion on during ingestion of a meal and off during the interdigestive period. A better understanding of the physiology of acid secretion in health and disease should eventually lead to improved therapies to prevent and treat acid-related disorders.

**Andres E, Perrin AE, Demangeat C. The syndrome of food-cobalamin malabsorption revisited in a department of internal medicine. A monocentric cohort study of 80 patients.** *Eur J Intern Med.* **2003** Jul;14(4):221-226.

Background: To date, only case reports or small studies have documented the syndrome of food-cobalamin malabsorption in specific populations of patients or situations. In this paper, we present the data from 80 unselected patients with cobalamin deficiency related to food-cobalamin malabsorption. Methods: We studied 80 patients with well-established food-cobalamin malabsorption who were extracted from an observational cohort study (1995-2000) of 127 consecutive patients with cobalamin deficiency and who were followed in a department of internal medicine. Results: The median age of patients was 66 years and the female to male ratio was 1.2. The mean hemoglobin level was  $113 \pm 27$  g/l (range 32-159 g/l) and the mean erythrocyte cell volume was  $95.4 \pm 12.3$  fl (range 55-140 fl). Mean serum vitamin B12 and homocysteine levels were  $153 \pm 74$  pg/ml (range 35-200 pg/ml) and  $20.6 \pm 15.7$   $\mu$ mol/l (range 8-97  $\mu$ mol/l), respectively. The main clinical findings noted were peripheral neuropathy (46.2%), stroke (12.5%), confusion or dementia (10%), asthenia (18.7%), leg edema (11.2%), and digestive disorders (7.5%). The commonest associated conditions were atrophic gastritis (39%) with evidence of *Helicobacter pylori* infection (12.2%) and alcohol abuse (13.7%). Three patients had Sjogren's syndrome and one had systemic sclerosis. Ten percent of all patients were on long-term metformin (10%) and 7.5% on acid-suppressive drugs. Correction of the serum vitamin B12 levels and hematological abnormalities was achieved equally well in all patients treated with either intramuscular or oral crystalline cyanocobalamin. Conclusion: This study suggests that food-cobalamin malabsorption may be the leading cause of vitamin B12 deficiency in adults. As other studies have also reported, the condition is often associated with neuro-psychiatric findings and with several other conditions. Oral and parenteral cobalamin appear to be equally effective in correcting serum B12 levels and hematological abnormalities and, in many cases, they also relieve symptoms.

Filioussi K, Bonovas S, Katsaros T. **Should we screen diabetic patients using biguanides for megaloblastic anaemia?** *Aust Fam Physician*. 2003 May;32(5):383-4. Background: Patients taking biguanides on a continuous basis sometimes develop vitamin B12 deficient megaloblastic anaemia. The prevalence of this side effect has not been estimated. Methods: We screened 600 patients with type 2 diabetes treated with biguanides (phenformin or metformin) for a mean of 11.8 years (SD: 3.6 years) with complete blood counts, red cell indices and red cell morphology. If this showed macrocytosis, we measured total serum vitamin B12 and antiparietal cells antibodies (APCA). Patients with macrocytosis and low serum vitamin B12 levels were treated with cyanocobalamin 1 mg injection daily for seven days. Results: 54 (9%) of the patients had megaloblastic anaemia with low serum total vitamin B12 levels, only three (0.5%) also had abnormally raised APCA. All 54 patients responded to cyanocobalamin with a reticulocyte increase within 10 days. Conclusion: Annual screening for megaloblastic anaemia in patients on long term treatment with biguanides may be worthwhile. The anaemia is easily remediable and does not necessitate withdrawal of the drug.

Fujita H, Narita T, Yoshioka N, Hosoba M, Ito S. **A case of megaloblastic anemia due to vitamin B12 deficiency precipitated in a totally gastrectomized type II diabetic patient following the introduction of metformin therapy.** *Endocr J*. 2003 Aug;50(4):483-4. No abstract available.

Andres E, Noel E, Kaltenbach G, Perrin AE, Vinzio S, Goichot B, Schlienger JL. **Metformin-associated vitamin B12 deficiency.** *Arch Intern Med*. 2002 Oct 28;162(19):2251-2. No abstract available

Heine RJ. **Does the vitamin B12 deficiency caused by metformin disappear again after stopping this drug?** *Ned Tijdschr Geneesk*. 2002 Nov 16;146(46):2213-4. Dutch. No abstract available.

Desouza C, Keebler M, McNamara DB, Fonseca V. **Drugs affecting homocysteine metabolism: impact on cardiovascular risk.** *Drugs*. 2002;62(4):605-16.

Gilligan MA. **Metformin and vitamin B12 deficiency.** *Arch Intern Med*. 2002 Feb 25;162(4):484-5. No abstract available.

Ruscini JM, Page RL 2nd, Valuck RJ. **Vitamin B(12) deficiency associated with histamine(2)-receptor antagonists and a proton-pump inhibitor.** *Ann Pharmacother*. 2002 May;36(5):812-6. Objective: **To report a case of vitamin B(12) deficiency associated with long-term use (approximately 4 1/2 y) of histamine(2) (H(2))-receptor antagonists and a proton-pump inhibitor (PPI) in a patient with gastroesophageal reflux.** Case Summary: A 78-year-old nonvegetarian white woman with symptomatic gastroesophageal reflux (GER) was started on cimetidine 300 mg 4 times daily in February 1990 and took various other antisecretory medications over the course of the next 4 1/2 years. She had a normal serum vitamin B(12) concentration of 413 pg/mL in August 1992. In June 1994, her serum vitamin B(12) concentration was found to be in the low normal range at 256 pg/mL. Biochemical markers of vitamin B(12)-dependent enzyme activity were measured at that time, and methylmalonic acid (MMA) and homocysteine (HCYS) were elevated at 757 nmol/L and 27.3 micromol/L, respectively. Serum folate was within the normal range at 4.9 ng/mL, and serum creatinine was slightly elevated at 1.4 mg/dL. MMA and HCYS concentrations decreased dramatically with oral replacement of vitamin B(12) 1000 microg/d, which confirmed vitamin B(12) deficiency. Oral replacement also demonstrated that the woman was able to adequately absorb nonprotein-bound vitamin B(12) from the gastrointestinal tract, suggesting that her deficiency was a result of food-cobalamin malabsorption. The accumulation of MMA and HCYS was not a consequence of renal dysfunction, since both metabolites dramatically decreased with vitamin B(12) replacement. Discussions: Malabsorption of dietary protein-bound vitamin B(12) has been demonstrated with the use of H(2)-receptor antagonists and PPIs. One previous case report of vitamin B(12) deficiency resulting from long-term use of omeprazole has been published. The malabsorption of dietary vitamin B(12) is thought to be a result of its impaired release from food protein, which requires gastric acid and pepsin as the initial step in the absorption process. **Conclusions: The use of H(2)-receptor antagonists and/or PPIs may impair the absorption of protein-bound dietary vitamin B(12) and could contribute to the development of vitamin B(12) deficiency with prolonged use. Patients taking these medications for extended periods of time, particularly >4 years, should be monitored for vitamin B(12) status.**

**CB comment: Italics above are mine. I would have suggested moving to simply prevent it with appropriate supplementation of B12, since monitoring regularly misses large numbers of deficient people.**

Mitchell SL, Rockwood K. **The association between antiulcer medication and initiation of cobalamin replacement in older persons.** *J Clin Epidemiol*. 2001 May;54(5):531-4. As chronic use of antiulcer medications might predispose older persons to cobalamin deficiency, we studied participants (> 65 years) in the clinical examination of the Canadian Study of Health and Aging to test the association between the use of an antiulcer medication (histamine-2 blocker or proton pump inhibitor) at baseline with initiation of cobalamin replacement during the 5 year follow-up period. Of 1054 eligible subjects, 125 (11.7%) were taking an antiulcer medication at baseline. At follow-up, 49 (4.6%) had started cobalamin replacement. Antiulcer medication use at baseline was significantly associated with the initiation of cobalamin therapy (odds ratio 2.56, 95% confidence interval 1.30-5.05), even after adjusting for age, gender and institutional residence (odds ratio 2.61, 95% confidence interval 1.31-5.23). There is an independent association between the use of antiulcer medication and initiation of cobalamin therapy. While the relationship is not unambiguously causal, this finding underscores the need for judicious prescribing of antiulcer medications for older persons.

**CB comment: Italics above are mine. While judicious prescribing is always appropriate it does not prevent B12 deficiency in the folks who are (judiciously) found to need to use proton pump inhibitors. Why can't we mention the idea of preventing the problem with appropriate supplementation?**

**Metformin-associated vitamin B12 deficiency.** *Arch Intern Med.* **2002** Oct 28;162(19):2251-2. No abstract available.

ter Heide H, Hendriks HJ, Heijmans H. **Are children with cystic fibrosis who are treated with a proton-pump inhibitor at risk for vitamin B(12) deficiency?** *J Pediatr Gastroenterol Nutr.* **2001** Sep;33(3):342-5. Background: In a recent study, the authors demonstrated the beneficial effect of proton-pump inhibitors (PPI) on fat malabsorption and bone mineral content in children with cystic fibrosis (CF). Prolonged use of PPI could result in vitamin B(12) deficiency as a consequence of impaired release of vitamin B(12) from food in a nonacid environment. The aim of this study was to evaluate the vitamin B 12 status of CF patients either treated with a PPI or not by measuring vitamin B(12) and homocysteine blood levels, the latter being a sensitive indicator of vitamin B(12) deficiency. Methods: The study population consisted of 20 CF patients, 11 patients treated with a PPI for at least 2 years and 9 patients not treated with a PPI, and 10 healthy, age-matched control participants. Homocysteine blood levels were measured by high-performance liquid chromatography, and vitamin B(12) levels were measured by a competitive protein-binding assay. Results: Vitamin B(12) levels were significantly higher in both CF groups compared with the control participants (PPI+, P = 0.02; PPI-, P = 0.009). There was no significant difference in vitamin B(12) levels between both CF groups. Homocysteine levels were normal and similar in all groups. Conclusions: *Cystic fibrosis patients treated with a PPI for at least 2 years show no signs of vitamin B(12) deficiency.*

**CB comment: Italics above are mine. It would have been very surprising to have found B12 deficiency in this situation, since children with CF are routinely supplemented with higher dose supplemental vitamins. So, rather than being interpreted as evidence that the proton pump inhibitors do not impair vitamin B12 absorption from food, it should be interpreted as showing that adequate provision of vitamin B12 in supplement form can protect against deficiency among persons using these medications.**

Jolobe OM. **Prevalence of hypochromia (without microcytosis) vs microcytosis (without hypochromia) in iron deficiency.** *Clinical & Laboratory Haematology.* 22(2):79-80, **2000** Apr. The usefulness of hypochromia (MCH deficiency) was examined in 365 geriatric patients aged 67-96 years with either one or both of these characteristics. Of these, 201 proved to be iron deficient with a serum ferritin of 18 mcg/l. There was a highly significant difference (P < 0.001) between the proportion of iron deficient patients with a mean corpuscular haemoglobin (MCH) < 26 pg (in the presence of a mean corpuscular volume (MCV) > 80 (fl) vs. counterparts with MCV < 80 fl (in the presence of MCH > 26 pg). *Fifteen per cent of the 201 iron deficient subjects were also shown to have coexisting vitamin B12 deficiency.* There was a comparable (16%) prevalence of this haematinic deficiency in the subgroup of 31 iron deficient patients with MCH < 26 pg in the presence of MCH > 80 fl.

**CB comment: Italics above are mine. This study shows that megaloblastic anemia as a marker of B12 deficiency can be masked by a concomitant iron deficiency, thus making its usefulness as a marker even less reliable. It is a very poor measure to use for screening in any case, since megaloblastic anemia is a very late-appearing symptom of vitamin B12 deficiency, and significant harm can be done long before the red cell size is affected.**

**Side effects. Calcium supplements help metformin users absorb vitamin B12.** *Treatmentupdate.* **2000** Oct;12(7):6-7. No abstract available.

Bauman WA, Shaw S, Jayatilleke E. **Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin.** *Diabetes Care.* **2000** Sep;23(9):1227-31.

Pautas E, Cherin P, De Jaeger C, Godeau P. **Vitamin B 12 deficiency in the aged.** *Presse Medicale.* 28(32):1767-70, **1999** Oct 23. A COMMON CONDITION: Vitamin B12 deficiency is common in the elderly. Search for deficiency should be undertaken whenever the clinical situation could lead to vitamin deficiency whether macrocytic anemia is present or not as its development may come late. **PATHOPHYSIOLOGICAL IMPLICATIONS: The potential relationships between degenerative neuropsychiatric disorders and cerebrovascular or cardiovascular disease, mainly via hyperhomocysteinemia, emphasize the importance of searching for vitamin B12 deficiency in the elderly. SPECIFIC CAUSES: In the elderly, it is important to recognize specific causes of vitamin B12 deficiency, mainly resulting from vitamin malabsorption.**

Bopp-Kistler I. Ruegger-Frey B. Grob D. Six P. **Vitamin B12 deficiency in geriatrics.** *Schweizerische Rundschau für Medizin Praxis.* 88(45):1867-75, **1999** Nov 4. **Cobalamin deficiency increases with advancing age. The cut-off point of serum concentration should be raised, because many elderly people with "normal" serum vitamin B12 concentrations are metabolically deficient in cobalamin.** The measurement of the metabolites homocysteine and/or methylmalonic acid is recommended. Cobalamin deficiency may result in a variety of atypical symptoms. Hematological changes typical of megaloblastic anemia are absent in a majority of patients with neuropsychiatric disorders. Generally underlying pernicious anemia is not the main cause of cobalamin deficiency in the elderly. Protein-bound cobalamin malabsorption due to atrophic gastritis with hypo- or achlorhydria is a common cause of cobalamin deficiency in elderly people. An important manifestation of cobalamin deficiency is cognitive impairment. Much controversy exists on the subject of the association of dementia of the Alzheimer type with cobalamin deficiency. In several studies dementia has been related to low serum cobalamin levels. **Physicians should be liberal of cobalamin therapy. The window of opportunity for effective intervention may be as short as one year from the onset of medical symptoms.** At last a compilation of recommendations is given.

Bradford GS. Taylor CT. **Omeprazole and vitamin B12 deficiency.** *Annals of Pharmacotherapy.* 33(5):641-3, **1999** May. The mainstay for cobalamin deficiency is correction of the underlying disorder and replacement therapy. Because the defect is often one of absorption, parenteral or intranasal routes are recommended. In most cases, replacement therapy is all that is needed. The vitamin preparation most commonly used is cyanocobalamin (also called vitamin B12), which has no known physiologic role but instead is converted to a biologically active form before it can be used by tissues. **The studies reviewed in this article clearly show that omeprazole therapy will decrease the absorption of vitamin B12 by preventing its cleavage from dietary proteins.** However, these data are insufficient to infer that clinically significant deficiency will occur over time. In fact, some of the studies suggest that the simple addition of juices or other acidic drinks into the diet may dramatically increase cobalamin absorption. Clearly, well-designed clinical trials are needed to evaluate this theory over an extended follow-up period to determine the clinical significance of omeprazole-associated vitamin B12 deficiency and possibly identify patients at risk for deficiency. **In conclusion, the possibility of dietary vitamin B12 malabsorption should be considered in patients receiving chronic omeprazole treatment and presenting with signs and symptoms of deficiency. All healthcare workers should be made aware of the potential clinical complications of omeprazole-associated vitamin B12 deficiency since it may go unrecognized and is easily corrected. This is particularly relevant for elderly patients with poor dietary intake of vitamin B12, impaired vitamin B12 stores, and certain gastrointestinal disorders.**

**CB comments from an earlier version of references regarding the above report:**

**I see a problem with this plan.**

1. They note that B12 deficiency often goes unrecognized.
2. In spite of this, the action suggested is to “watch for signs and symptoms of deficiency” before doing anything, since not everyone may be in fact deficient.
3. This is going to miss a bunch of folks. Also, some of the “signs and symptoms” are relatively late-appearing symptoms like macrocytosis. By then, one can no longer efficiently make DNA, and some neurologic damage may not be totally repairable.
4. Why not simply assure adequacy by suggesting that patients on this drug simply take vitamin B12 in a cheap and readily available form that does not require acid for absorption (e.g. in a multivitamin – no protein molecule attached) and prevent the whole thing? It is cheap, safe and helpful in a bunch of other situations at the same time. I don’t get it.
5. They note that they will have to wait a number of years to see how many people actually become deficient, so the “present study” cannot answer this question. True. But just because this study is unable to measure a potentially seriously negative clinical outcome, I am not sure that waiting to see how many people are injured down the road before suggesting benign supplementation is the moral high ground here. Prevention is a snap and the potential injury associated with deficiency is too great.

Baik HW. Russell RM. **Vitamin B12 deficiency in the elderly,** *Annual Review of Nutrition.* 19:357-77, **1999.** **Vitamin B12 deficiency is estimated to affect 10%-15% of people over the age of 60, and the laboratory diagnosis is usually based on low serum vitamin B12 levels or elevated serum methylmalonic acid and homocysteine levels.** Although elderly people with low vitamin B12 status frequently lack the classical signs and symptoms of vitamin B12 deficiency, e.g. megaloblastic anemia, precise evaluation and treatment in this population is important. **Absorption of crystalline vitamin B12 does not decline with advancing age.** However, compared with the younger population, absorption of protein-bound vitamin B12 is decreased in the elderly, owing to a high prevalence of atrophic gastritis in this age group. Atrophic gastritis results in a low acid-pepsin secretion by the gastric mucosa, which in turn results in a reduced release of free vitamin B12 from food proteins. Furthermore, hypochlorhydria in atrophic gastritis results in bacterial overgrowth of the stomach and small intestine, and these bacteria may bind vitamin B12 for their own use. **The ability to absorb crystalline vitamin B12 remains intact in older people with atrophic gastritis. The 1998 recommended daily allowance for vitamin B12 is 2.4 micrograms, but elderly people should try to obtain their vitamin B12 from either supplements or fortified foods (e.g. fortified ready-to-eat breakfast cereals) to ensure adequate absorption from the gastrointestinal tract.** Because the American food supply is now being fortified with folic acid, concern is increasing about neurologic exacerbation in individuals with marginal vitamin B12 status and high-dose folate intake.

Shaw JT, McWhinney B, Tate JR. **Plasma homocysteine levels in indigenous Australians.** *Med J Aust.* **1999** ;170(1):19-22.

*Nutrition & Health.* 12(4):215-26, **1998.** **Vitamin B12 deficiency damages nerve cells and aggravates nervous system disorders even in the absence of evidence of anaemia.** Prevalence of B12 deficiency increases with age especially over 65 and is frequently associated with Alzheimer's disease. **Recent American surveys record a higher prevalence of B12 deficiency and of undiagnosed and untreated pernicious anaemia in the elderly than reported earlier. B12 deficiency is also reported to be a risk factor for heart disease, stroke and accelerated ageing.**

Nilsson-Ehle H. **Age-related changes in cobalamin (vitamin B12) handling. Implications for therapy.** *Drugs & Aging.* 12(4):277-92, **1998** Apr **Cobalamin (vitamin B12) deficiency is more common in the elderly than in younger patients. This is because of the increased prevalence of cobalamin malabsorption in this age group, which is mainly caused by (autoimmune) atrophic body gastritis. Cobalamin supplementation is affordable and nontoxic, and it may prevent irreversible neurological damage if started early. Elderly individuals with cobalamin deficiency may present with neuropsychiatric or metabolic deficiencies, without frank macrocytic anaemia.** An investigation of symptoms and/or signs includes the diagnosis of deficiency as well as any underlying cause. Deficiency states can still exist even when serum cobalamin levels are higher than the traditional lower reference limit. Cobalamin-responsive elevations of serum methylmalonic acid (MMA) and homocysteine are helpful laboratory tools for the diagnosis. The health-related reference ranges for homocysteine and MMA appear to vary with age and gender. Atrophic body gastritis is indirectly diagnosed by measuring serum levels of gastrin and pepsinogens, and it may cause dietary cobalamin malabsorption despite a normal traditional Schilling's test. The use of gastroscopy may also be considered to diagnose dysplasia, bacterial overgrowth and intestinal villous atrophy in healthy patients with atrophic body gastritis or concomitant iron or folic acid deficiency. Elderly patients respond to cobalamin treatment as fully as younger patients, with complete haematological recovery and complete or good partial resolution of neurological deficits. Chronic dementia responds poorly but should, nevertheless, be treated if there is a metabolic deficiency (as indicated by elevated homocysteine and/or MMA levels). Patients who are at risk from cobalamin deficiency include those with a gastrointestinal predisposition (e.g. atrophic body gastritis or previous partial gastrectomy), autoimmune disorders [type 1 (insulin-dependent) diabetes mellitus and thyroid disorders], those receiving long term therapy with gastric acid inhibitors or biguanides, and those undergoing nitrous oxide anaesthesia. To date, inadequate cobalamin intake has not proven to be a major risk factor. Intervention trials of cobalamin, folic acid and pyridoxine (vitamin B6) in unselected elderly populations are currently under way. [Ref: 165]

Aarsand AK, Carlsen SM. **Folate administration reduces circulating homocysteine levels in NIDDM patients on long-term metformin treatment.** *J Intern Med.* **1998** Aug;244(2):169-74.

Riordan SM, McIver CJ, Wakefield D.. **Small intestinal bacterial overgrowth in the symptomatic elderly.**

*American Journal of Gastroenterology.* 92(1):47-51, **1997** Jan. **OBJECTIVE:** 1) To determine the prevalence of small intestinal overgrowth with colonic-type bacteria in symptomatic elderly subjects, particularly those without important "clues" such as clinically apparent predisposition or vitamin B12 deficiency, and 2) to investigate defense mechanisms such as gastric acidity, small intestinal motility, and luminal IgA in this setting. **METHODS:** Fifty-two symptomatic subjects without vitamin B12 deficiency or clinically apparent predisposition to bacterial overgrowth or disturbed mucosal immunity, including 22 subjects  $\geq$  75 yr old, underwent culture of small intestinal luminal secretions. Indicator paper was used to measure fasting gastric pH. The presence of bacteria of confirmed nonsalivary origin in small intestinal secretions served as an index of small intestinal dysmotility. Small intestinal luminal IgA concentrations were measured by radial immunodiffusion. **RESULTS:** Small intestinal overgrowth with colonic-type flora was not present in any subject investigated for dyspepsia, irrespective of age. In subjects with chronic diarrhea, anorexia, or nausea, overgrowth with colonic-type flora (Enterobacteriaceae) was present in 0/12 (0%), 1/10 (10.0%), and 9/14 (64.3%) subjects aged  $<$  50 yr, 50-74 yr, and  $\geq$  75 yr, respectively. Enterobacteriaceae were not concurrently recovered from saliva of any subject  $\geq$  75 yr old with small intestinal overgrowth with these bacteria. Fasting hypochlorhydria was present in only 1/9 (11.1%) such subjects. Luminal IgA concentrations were significantly greater in subjects  $\geq$  75 yr old with bacterial overgrowth than in culture-negative subjects ( $p < 0.003$ ). **CONCLUSIONS: Small intestinal overgrowth with colonic-type bacterial should be considered in subjects  $\geq$  75 yr old with chronic diarrhea, anorexia, or nausea, even in the absence of clues such as clinically apparent predisposition or vitamin B12 deficiency.** Small intestinal dysmotility, rather than fasting hypochlorhydria or mucosal immunosenescence, probably is responsible for the prevalence of bacterial overgrowth in this group.