

Vitamin B12 Clinical Pearls

AGE-RELATED MACULAR DEGENERATION - Vitamin - A study in Arch Ophthalmol, 2001;119:1417-1436 concluded that supplementation of vitamin C at 500 mg, vitamin E at 400 IU, and beta-carotene at 15 mg with zinc oxide at 80 mg should be considered in patients with extensive intermediate-size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced age-related macular degeneration or vision loss caused by age-related macular degeneration in 1 eye. It is noted in the body of this article that 57% of the study participants were already taking antioxidant vitamins before enrolling in this study, and an additional 13% who were not taking supplements chose to take the multivitamin mineral supplement Centrum. Therefore, 67% of those in the trial also concurrently took Centrum. The authors question whether concurrent taking of Centrum, which contains levels of vitamin C, vitamin E, beta-carotene and zinc, as well as other micronutrients, such as vitamins D, E, K B6 and B12, thiamin, riboflavin, niacin, folic acid, biotin, pantothenic acid, calcium, iron, phosphorus, iodine, magnesium, selenium, copper, manganese, chromium, molybdenum, chloride, potassium, boron, nickel, silicon, tin, vanadium and now lutein, could be the reason why the antioxidants worked in those patients also taking Centrum. The authors stated that the treatment effect of the study formulations was in the beneficial direction for both the age-related macular degeneration patients who took and didn't take Centrum, but they state the data are "not shown" and that "these comparisons are underpowered." The authors state that if one believes the conclusion of this study, one should probably take a Centrum in addition to the specific supplements recommended. "High-Dose Supplements for Age-Related Macular Degeneration: Did You Leave Out Centrum?" Abramson DH, Abramson HS, Arch Ophthalmol, November 2002;120:1602. 40040

AGING - Cobalamin, Vitamin B12 - In a study of 186 women and 56 men ranging from 72 to 73 years of age, 176 individuals did not take cobalamin supplements, while 66 subjects did take cobalamin supplements. It was found that serum levels of cobalamin were significantly higher in individuals who took oral cobalamin supplements, ranging from 2.0 to 37.5 mcg/day. Serum levels of the metabolites methylmalonic acid, homocysteine and methylcitric acid were lower in subjects on cobalamin supplements. Intake of low-dose oral supplements of cobalamin significantly reduced the odds of low cobalamin levels or high methylmalonic acid. There was a dose-dependent relationship between cobalamin supplementation and these biochemical parameters. "Is Low-Dose Oral Cobalamin Enough to Normalize Cobalamin Function in Older People?" Garcia A, Paris-Pombo A, et al, J Am Geriatr Soc, August 2002;50:1401-1404. (Address: Angela Garcia, MD, PhD, FRCP(C), E-mail: garciaa@pccc.kari.net) 39871

AGING - Folic Acid, Vitamin B12 - In studying 1,562 elderly male and female subjects for vitamin B12 and folate deficiency, total homocysteine and methylmalonic acid cutoff values at >15.0 umol/l for total homocysteine and >0.35 umol/l for methylmalonic acid identified individuals with normal or elevated risk. In individuals who were between 65 and 74 years of age and ≥75 years of age, respectively, there were approximately 10%

and 20% of the subjects at high risk for vitamin B12 deficiency. About 10% and 20%, respectively, were also at high risk for folate deficiency. About 10% of the individuals had both vitamin B12 and folate deficiency. **"Screening for Vitamin B-12 and Folate Deficiency in Older Persons,"** Clarke R, Refsum H, Birks J, et al, Am J Clin Nutr, 2003;77:1241-1247. (Address: Robert Clarke, E-mail: robert.clarke@cts.ox.ac.uk) 40489

AGING - Homocysteine - In evaluating 196 subjects over 65 years of age, mean homocysteine levels were 13.2 umol/l. The mean level for men was 15.0 umol/l and for women 12.3 umol/l. Mean serum folic acid levels were 4.9 ng/ml and mean vitamin B12 levels were 384.8 pg/ml. Elevated homocysteine levels were found in 69.8% of all subjects, with 76.2% of the men and 66.4% of the women having elevated homocysteine levels. **"Prevalence of Hyperhomocysteinemia in an Elderly Population,"** Janson JJ, Galarza CR, et al, Am J Hypertens, 2002;15:394-397. (Address: Dr. Jorge J. Janson, E-mail: jjanson@intramed.net.ar) 39805

AGING - Hyperhomocysteinemia, Vitamin B12 - In 103 individuals (mean age 76.4 years), of whom 80% were female, 68% white and 32% African-American, serum vitamin B12 at levels < 258 pmol/l and methylmalonic acid at levels > 271 nmol/l were found in 23%, which defined them as vitamin B12-deficient. Mean serum folate was high, and no individual had serum folate levels < 6.8 nmol/l. Mean total homocysteine was 17.6 umol/l in the vitamin B12-deficient subjects and 10.8 umol/l in those who were nondeficient. Factors that affected high total homocysteine levels were vitamin B12 deficiency, high serum creatinine, and low red blood cell folate. Those with vitamin B12 deficiency were more likely to have poor cognition (58% vs 20%, respectively) and anemia (38% vs 18%, respectively). High-dose oral vitamin B12 at 2.5 mg daily along with a multivitamin supplement, which included folic acid at 400 mcg, vitamin B6 at 2 mg, vitamin D at 400 IU, calcium at 450 mg, ferrous fumarate at 27 mg and 100% of the recommended daily allowances for vitamins A, C, E, B12, thiamin, riboflavin, niacin, pantothenic acid and zinc, lowered mean methylmalonic acid and total homocysteine levels by 49% and 32%, respectively. Vitamin B12-deficiency was associated with poor cognition, anemia and hyperhomocysteinemia. **"Hyperhomocysteinemia and Vitamin B-12 Deficiency in Elderly Using Title IIIc Nutrition Services,"** Johnson MA, Hawthorne NA, Brackett WR, et al, Am J Clin Nutr, 2003;77:211- 220. (Address: Sally P. Stabler, E-mail: sally.stabler@UCHSC.edu) 40170

AGING - Vitamin B12 - In one study, more than 12% of noninstitutionalized elderly subjects were vitamin B12 deficient. There is considerable research indicating that oral vitamin B12 replacement is of benefit. Vitamin B12 absorption is a complex multi-step process which requires an acidic environment, intrinsic factor and a transport protein, such as transcobalamin II. It is absorbed in the ileum part of the small intestine. Vitamin B12 is essential for two major reactions in the human body: the enzymatic conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA in the Krebs cycle and the conversion of the amino acid homocysteine to methionine. Cobalamin is essential for the conversion of methyltetrahydrofolate to tetrahydrofolate for DNA production. If this

does not occur, megaloblastic changes occur in the red blood cell. Causes of vitamin B12 deficiency include achlorhydria or hypochlorhydria; insufficient protease in the duodenum; lack of intrinsic factor secreted by the gut mucosa; and high demand states, such as hyperthyroidism, cancer or bacterial overgrowth. About 2 mg of vitamin B12 are stored in the liver and another 2 mg in other parts of the body. Lack of intrinsic factor leads to deficiency in 3-5 years. Deficiency in strict vegetarians develops in 10-20 years. Insufficient vitamin B12 can disrupt the conversion of homocysteine to methionine, impairing myelin sheath production and initially causing the demyelination followed by axonal degeneration and neuronal death. Drugs such as metformin hydrochloric acid impair vitamin B12 absorption in 10-30% of diabetic patients but this can be reversed with calcium supplementation. Slow-release potassium chloride may inhibit absorption. Long-term therapy with proton pump inhibitors such as omeprazole and H2-receptor antagonists such as cimetidine can significantly reduce food-bound cobalamin absorption. Laboratory values of vitamin B12 may correlate poorly with clinical significance. Homocysteine and methylmalonic acid can accumulate with vitamin B12 deficiency. Initial testing should include a serum vitamin B12 level. Secondary tests are methylmalonic acid and homocysteine, with methylmalonic acid being more specific. One percent to 2% of oral vitamin B12 is absorbed by passive diffusion. A dose of 1,000 mcg/day is recommended for replacement doses, whereas 100-250 mcg is enough to maintain stores. An oral daily dose of 2,000 mcg of vitamin B12 compared with nine 1,000-mcg intramuscular injections over 3 months showed that the oral regimen resulted in higher vitamin B12 levels and lower methylmalonic acid levels at 4 months.

"Vitamin B12 Deficiency in the Elderly: A New Look at Treatment," Hamrick I, Family Practice Recertification, June 2003;25(6):16-26. 40619

AGING - Vitamin B12 - Food-cobalamin malabsorption can occur in atrophic gastritis, Helicobacter pylori infection, partial gastrectomy, gastric bypass surgery, vagotomy, alcohol abuse, cystic fibrosis, achlorhydria, tropical sprue, Olgivy syndrome, aging, with acid suppressive drugs, and from idiopathic causes. Between 250 and 1,000 mcg/day of cyanocobalamin has been shown to improve serum vitamin B12 and total homocysteine levels and improve hematological parameters in short-term and long-term follow-up. Taking 1,000 mcg/day has been shown to improve serum vitamin B12 and lower total homocysteine levels and improve hematological parameters within 1 month and at follow-up. **"Vitamin B12 Deficiency in Older Adults,"** Kaltenbach G, Dharmarajan TS, et al, Geriatrics, July 2003;58(7):12-13. 40745

ANEMIA - Folic Acid, Vitamin B12 - In a study of 1,573 individuals with low vitamin B12 levels (<258 pmol/l), the proportion without anemia did not increase significantly from the prefortification period (39.2%) to the period of optimal fortification (45.5%) and the postfortification period (37.6%). These findings did not change when the analysis was limited to those who were 60 years of age or older or for those with a low vitamin B12 level of <150 pmol/l. Folic acid exposure has increased dramatically since food fortification began, but there is no evidence of an increase in low vitamin B12 levels without anemia. Folic acid fortification of food is probably not a major increased risk for masking vitamin B12 deficiency. **"Low Vitamin B12 Concentrations in Patients Without Anemia: The Effect of Folic Acid Fortification of Grain,"** Mills JL, Von

Kohorn I, Conley MR, et al, Am J Clin Nutr, 2003;77:1474-1477. (Address: James L. Mills, E-mail: jamesmills@nih.gov) 40583

ATHEROSCLEROSIS - Homocysteine - Elevated plasma homocysteine levels can be considered an independent risk factor for atherothrombotic disease. Homocysteine is an intermediate sulfur- containing amino acid that is formed during the intracellular metabolism of methionine, which is an essential amino acid supplied by dietary proteins. When homocysteine is formed, it is recycled to methionine after remethylation by 2 different pathways. The first involves methionine synthase, which is an enzyme that uses vitamin B12 as an essential cofactor and -methyl-tetrahydrofolate as the methyl donor. The second pathway, which occurs in hepatic tissue, involves the enzyme betaine-homocysteine methyltransferase. Homocysteine may be converted to cystathionine by cystathionine beta-synthase, which is a vitamin B6-dependent enzyme. Cystathionine is hydrolyzed to form cysteine. Cysteine can be used to synthesize the antioxidant glutathione or may be metabolized to sulfate and excreted in the urine. Plasma levels of homocysteine refer to the total pool of homocysteine, since there is very little free homocysteine. Moderate levels of elevated homocysteine are 16-30 umol/l; intermediate, 31-100 umol/l; and severe, >100 umol/l. Nutritional deficiencies of vitamin B12, B6 and folate may be a reason for mild hyperhomocysteinemia. Mild elevation of homocysteine may promote the accumulation of macrophages, which contribute to proinflammatory and proatherosclerotic responses. Elevated homocysteine may also induce endothelial dysfunction; increase vascular smooth muscle cell proliferation and platelet activation; promote lipoprotein oxidation and enhance coagulability; and increase the synthesis of cholesterol in hepatocytes. Mild hyperhomocysteinemia might promote atherogenesis by stimulating infiltration of leukocytes to sites of vascular injury. **"Homocysteine, A Proinflammatory and Proatherosclerotic Factor: Role of Intracellular Reactive Oxygen Species,"** Schini- Kerth VB, Circ Res, August 22, 2003;93:271-273. (Address: Valerie B. Schini-Kerth, PhD, E-mail: schini@aspirine.u-strasbg.fr) 40871

AUTISM - Intestinal Permeability - It has been noted in one study that autistic children had an increase in ileal lymphoid nodular hyperplasia. It has also been noted anecdotally that milk and wheat elimination have improved some autistic symptoms. Elimination diets of one or either of these two substances have shown benefit. It has been hypothesized that the measles-mumps- rubella (MMR) vaccine may be a potential cause of triggering autism, but this has been debated. Also, vaccines containing thimerosal, an ethylmercury sodium salt, may provide toxic amounts of mercury that may affect the immune system of the gut. A reduction in secretin secretion may lead to hyperacidity of the intestinal lumen, which may alter gut function. There may be an intestinal malabsorption of vitamin B12, which may also impair nerve function and may affect autistic children. Vitamin B12 absorption has been noted to be significantly reduced in some studies of autistic children. Rigorous study on the role of gut function in autism should be noted. There is evidence that autistic children have increased intestinal permeability. **"Intestinal Pathophysiology in Autism,"** White JF, Exp Biol Med, 2003;228:639-649. (Address: John F. White, E-mail: jfwhite@physio.emory.edu) 40603

CANCER - Adenoma, Colorectal, Folate - In a study of 34 men and 42 women (mean age 58.0 years) who acted as controls compared with 23 men and 12 women (mean age 66.4 years) with colorectal adenomas and 13 men and 15 women (mean age 68.9 years) with colorectal cancer, those with cancer had a 26% lower folate status and a 21% lower serum vitamin B12 level compared with controls. [3H] methyl incorporation into colonic DNA was 26% higher in patients with adenoma and 30% higher in patients with cancer compared with controls. Increased folate status was associated with a reduced risk of colon cancer. Colonic and leukocyte DNA hypomethylation were associated with an increased risk of adenoma and a non-significantly increased risk for cancer. **"Folate Status, Genomic DNA Hypomethylation, and Risk of Colorectal Adenoma and Cancer: A Case Control Study,"** Pufulete M, Al-Ghnam R, et al, Gastroenterology, May 2003;124(5):1240-1248. (Address: Maria Pufulete, PhD, (FAX) 44 (020) 7848-4185, E-mail: maria.pufulete@kcl.ac.uk) 40747

CANCER - Breast, Folic Acid, Homocysteine, Vitamin B6, Vitamin B12 - In evaluating blood samples from 32,826 women between 1989 and 1990, there were 712 breast cancer patients identified who were compared with 712 individually matched control subjects. The relative risk comparing women in the highest quintile of plasma folate with those in the lowest was 0.73 for breast cancer. The inverse association between plasma folate and breast cancer risk was highly statistically significant among women consuming at least 15 g/day of alcohol, which is approximately 1 drink per day, in contrast with women consuming <15 g/day. The multivariable relative risk comparing women in the highest quintile of plasma vitamin B6 levels with those in the lowest quintile was 0.70. Plasma vitamin B12 levels were inversely associated with breast cancer risk among premenopausal women but not among postmenopausal women. Plasma homocysteine was not associated with breast cancer risk. **"Plasma Folate, Vitamin B6, Vitamin B12, Homocysteine, and Risk of Breast Cancer,"** Zhang SM, Willett WC, Selhub J, et al, J Natl Cancer Inst, March 5, 2003;95(5):373-380. (Address: Shumin M. Zhang, MD, ScD, E-mail: Shumin.Zhang@channing.harvard.edu) 40480

CANCER - Colorectal, Adenoma - In a study of 23 male and 12 female subjects, mean age of 66.4 years, with colorectal adenomas, 13 men and 15 women, mean age of 68.9 years, with cancer compared to 34 men and 42 women, mean age of 58 years, who acted as controls, cancer patients had 26% lower blood folate levels and a 21% lower serum vitamin B12 level compared with the control subjects. [3H]methyl incorporation into colonic DNA was 20% higher in the subjects with adenomas and 30% higher in the patients with cancer compared to the control subjects. High folate levels were associated with a reduced risk for cancer. Colonic and leukocyte DNA hypomethylation were associated with an increased risk for adenoma and a nonsignificant risk for cancer. The combination of low folate levels and DNA hypomethylation are associated with colorectal cancer: **"Folate Status, Genomic DNA Hypomethylation, and Risk of Colorectal Adenoma and Cancer: A Case Control Study,"** Pufulete M, Al-Ghnam R, et al, Gastroenterology, 2003;124:1240-1248. (Address: Maria Pufulete, PhD, (Fax) 44 020 7848 4185, E-mail: maria.pufulete@kcl.ac.uk) 40527

CANCER - Colorectal, Folate, Vitamin B6, Vitamin B12 - In a study of 41,836 women who were between 55 and 69 years of age who completed a survey, there were 598 cases of colon cancer and 123 cases of rectal cancer over 13 years of follow-up. There were no independent associations of folate, methionine or vitamins B6 and B12 derived from food frequency questionnaires. The relative risk of rectal cancer increased progressively with increasing intake of vitamin B6. The relative risk for cancer of the proximal colon was lower among those with high folate and high vitamin B12 intake or high folate and high vitamin B6 intake compared with those with the lowest intake of these nutrients. The incidence of cancer of the proximal colon was lower among those with high folate and low alcohol intake. This study showed limited support for the association between dietary factors that are involved in DNA methylation and the risk of cancers of the colon and rectum. **"Relationship of Folate, Vitamin B-6, Vitamin B-12, and Methionine Intake to Incidence of Colorectal Cancers,"** Harnack L, Jacobs DR, et al, Nutr Cancer, 2002;43(2):152-158. 40378

CANCER - Gastrointestinal, Stomach, Folic Acid - This study examined 26 male and 18 female subjects with atrophic gastritis (mean age 56.6 years) who took 20 mg/day of folic acid plus vitamin B12 at 1 mg intramuscularly per month for 1 year, then 20 mg of folic acid, 2 times/week, plus 1 mg of vitamin B12 every 3 months for the next year; 38 male and 23 female subjects (mean age 55.0 years) who took 30 mg of natural beta-carotene for the first year, then 30 mg, 2 times/week for the next; 35 male and 22 female subjects (mean age 54.9 years) who took synthetic beta-carotene at 30 mg/day for the first year, then 30 mg, 2 times/week for the next; and 38 male and 16 female subjects (mean age 57.1 years) who took placebo. Subjects were followed-up from 1994 to 2001, and a total of 7 cases of gastrointestinal cancers were diagnosed (3 stomach, 1 colon and 1 esophageal) in the placebo group; 1 stomach cancer in both the synthetic and natural beta-carotene groups; and no cancer in the folic acid group. There were significant reductions in gastrointestinal cancers in the folic acid group compared with placebo. There was a similar trend in both the natural beta-carotene and synthetic beta-carotene groups. These 3 intervention groups had a highly significant reduction in occurrence of gastric cancer compared with placebo. The folic acid group showed improvement of the gastric mucosal lesions, with more patients showing lesions reversed or stable atrophy and inflammation, reversed intestinal metaplasia at the end of the follow-up, and reversed dysplasia at 12 months. No side effects were noted in the folic acid group. **"The Effect of Folic Acid on the Development of Stomach and Other Gastrointestinal Cancers,"** Zhu S, Mason J, Shi Y, et al, Chin Med J, 2003;116(1):15-19. (Address: Dr. Zhu Shunshi, (FAX) 86-21-63136856) 40792

CARDIOVASCULAR DISEASE - Antioxidant, Homocysteine - In 1,139 women and 931 men who were between 35 and 60 years of age, subjects were participants of the Supplementation with Antioxidant Vitamins and Minerals Study. The mean total homocysteine level was 8.74 umol/l in women and 10.82 umol/l in men. In women, total homocysteine was positively related to age, apolipoprotein B, serum triglycerides, fasting glucose, and coffee and alcohol consumption, and was inversely associated with red blood cell folate levels and plasma vitamin B12 and vitamin B6 intakes. In men, total homocysteine levels were positively associated with body mass index, blood pressure,

serum triglycerides, fasting glucose and energy intake, and inversely associated with physical activity, red blood cell folate, plasma vitamin B12 and dietary fiber, folate and vitamin B6 intakes. To lower total homocysteine levels, reducing coffee and alcohol consumption may be important in women, and in men, increasing physical activity, dietary fiber and folate intake may be important. **"Homocysteine, Cardiovascular Disease Risk Factors, and Habitual Diet in the French Supplementation With Antioxidant Vitamins and Minerals Study,"** Mennen LI, de Courcy GP, Guillard J- C, et al, *Am J Clin Nutr*, 2002;76:1279-1289. (Address: L. I. Mennen, ISTNA/CNAM, 5 rue de Vertbois, 75003 Paris, France, E-mail: s_mennen@vnam.cnam.fr) 40079

CARDIOVASCULAR DISEASE - Folate, Vitamin B12 - In a study of an initial cohort of 1,419 men (mean age 48.4 years) and 1,531 women (mean age 47.9 years) with some cardiovascular disease compared with 1,113 men (mean age 46.6 years) and 1,201 women (mean age 45.9 years) who were free of cardiovascular disease, 213 men and 159 women died from coronary heart disease, and 342 men and 302 women died from cardiovascular disease. Serum and red cell folate levels showed a moderate positive correlation, with regard to cardiovascular disease, while red cell folate and serum vitamin B12 levels were not strongly correlated with each other or with other risk factors. After adjusting for variables, there was no independent association between folate and vitamin B12 concentrations and death from coronary heart disease or cardiovascular disease in the full cohort or the subcohort with no cardiovascular disease at baseline. The hazard ratio for death from cardiovascular disease in the lowest vs highest categories of red cell folate concentration was 1.05 in men and 1.10 in women, suggesting that lower folate and vitamin B12 levels do not increase the risk of fatal cardiovascular disease in the general population. **"Folate and Vitamin B-12 and Risk of Fatal Cardiovascular Disease: Cohort Study From Busselton, Western Australia,"** Hung J, Beilby JP, et al, *BMJ*, January 18, 2003;326:131-136. (Address: J. Hung, E- mail: jhung@cyllene.uwa.edu.au) 40424

COGNITION - Homocysteine, Vitamin - Vitamin B12 and folate are necessary for adequate methylation by S-adenosylmethionine in the synthesis of neurotransmitters, myelin and phosphatidylcholine, as well as other compounds important for the nervous system. Mental symptoms have been shown to clear significantly and rapidly in patients with severe vitamin B12 deficiency following supplementation. Vitamin B12 has been shown to improve cognitive performance and abnormalities on electroencephalograms in vitamin B12-deficient elderly subjects. In 10-20% of seniors with metabolic evidence of vitamin B12 deficiency, subjects may benefit greatly from replacement. If vitamin B12 deficiency is suspected in an individual with hyperhomocysteinemia, it would be appropriate to treat that person with high doses of oral or parenteral vitamin B12 because vitamin B12 deficiency can result in central nervous system demyelination. Over-the-counter vitamin therapy can improve folate and vitamin B6 status. High-dose vitamin B12 supplements are required for the normalization of methylmalonic acid levels. **"Vitamins, Homocysteine, and Cognition,"** Stabler SP, *Am J Clin Nutr*, 2003;78:359-360. (Address: Sally P. Stabler, E-mail: sally.stabler@uchsc.edu) 40883

CORONARY ARTERY/HEART DISEASE - Folic Acid, Restenosis, Vitamin B6, Vitamin B12 - In a randomized, double-blind, placebo-controlled trial in which 79 males and 21 females (mean age of 63.4 years) after percutaneous coronary intervention received 1 mg of folic acid, 400 mcg of vitamin B12, and 10 mg of vitamin B6 daily, compared to 82 males and 18 females (mean age of 61.8 years) who received a placebo daily for 6 months, the composite end-point of major adverse events was significantly lower at 1 year in patients treated with the homocysteine-lowering therapy of B-vitamins at 15.4% versus 22.8%. This was primarily due to a reduction in the rate of target lesion revascularization. There was a nonsignificant trend toward fewer deaths at 1.5% vs. 2.8%, and nonfatal myocardial infarctions at 2.6% vs. 4.3% with homocysteine-lowering therapy. **"Effect of Homocysteine-Lowering Therapy With Folic Acid, Vitamin B12, Vitamin B6 on Clinical Outcome After Percutaneous Coronary Intervention. The Swiss Heart Study: A Randomized Controlled Trial,"** Schnyder G, Roffi M, et al, JAMA, August 28, 2002;288(8):973-979. (Address: Guido Schnyder, MD, E-mail: g.schnyder@lycos.com) 39748

DEMENTIA - Delirium, Vitamin B12 - This is a case report of a 52-year-old with organic psychosis who was admitted to the hospital with a 2-month history of disturbances of memory, depressive mood, apathy, and temporary disorientation. Vitamin B12 replacement therapy with hydroxycobalamin at 1,000 mcg/day for 10 days was administered, and then the patient was given monthly injections. One week after the vitamin B12 therapy was started, the patient's consciousness became clear, he became quiet and calm, and he had clear speech and a stable gait. The vitamin B12 levels rose to 746 pg/ml and folate was 11 ng/ml. The patient's electroencephalographic reading was within the normal limits, and the Mini-Mental State Examination scores reached 28. **"Acute Dementia With Delirium Due to Vitamin B12 Deficiency: A Case Report,"** Lerner V, Kanevsky M, Int J Psychiatry Med, 2002;32(2):215-220. (Address: Vladimir Lerner, MD, PhD, E-mail: lernervld@yahoo.com) 40090

DEMENTIA - Homocysteine, Vitamin - In a study of 149 patients at high risk for dementia, subjects were randomized to receive either low-dose aspirin at 81 mg or placebo; and folic acid at 2 mg plus vitamin B12 at 1 mg or placebo; and vitamin E at 500 mg plus vitamin C at 200 mg or placebo for a 12-week trial. Prior to treatment, cognitive function was inversely related with homocysteine and with urinary thromboxane and isoprostane, which were independent of age. Aspirin was associated with a median reduction in 11-dehydrothromboxane B2 of 73%. Vitamins B12 at 1 mg and folic acid at 2 mg lowered plasma homocysteine levels by 30%, and antioxidant vitamins lowered isoprostane excretion by 26%. There was no effect of any treatment on cognitive function. **"Effect of Vitamins and Aspirin on Markers of Platelet Activation, Oxidative Stress and Homocysteine in People at High Risk of Dementia,"** Clarke R, et al, J Intern Med, 2003;254:67-75. (Address: Dr. Robert Clarke, (FAX) +44 (0) 1865 558817, E-mail: robert.clarke@ctsu.ox.ac.uk) 40722

DEPRESSION - Folate, Homocysteine, Vitamin B12 - In a study of 278 individuals with depressive symptoms, which included 112 with depressive disorders, and 416 randomly selected control subjects, elevated homocysteine levels, vitamin B12 deficiency, and to a

lesser extent, folate deficiency were all related to depressive disorders, but in the case of vitamin B12, this appeared to be an independent association. Vitamin B12 may be causally related to depression, whereas the relation to folate may be due to physical comorbidity. "Vitamin B12, Folate, and Homocysteine in Depression: The Rotterdam Study," Tiemeier H, Breteler MMB, et al, Am J Psychiatry, December 2002;159:2099-2101. (Address: Dr. Breteler, E-mail: breteler@epib.fgg.eur.nl) 40288

DEPRESSION - Folate, Homocysteine, Vitamin B12 - In 5,948 individuals who were between 46 and 49 years of age (mean age 47.4 years) and 70 and 74 years of age (mean age 71.9 years), subjects were evaluated by the Hospital Anxiety and Depression Scale. Hyperhomocysteinemia, which was defined as homocysteine levels ≥ 15 $\mu\text{mol/l}$ and the T/T methylenetetrahydrofolate reductase genotype, but not low plasma folate or vitamin B12 levels, were significantly related to depression without comorbid anxiety disorder. Plasma folate levels were inversely associated with depression only in a subgroup of middle-aged women. This study suggests that there is impaired 1-carbon metabolism in depression. **"Folate, Vitamin B12, Homocysteine, and the MTHFR 677C/T**

Polymorphism in Anxiety and Depression: The Hordaland Homocysteine Study," Bjelland I, Tell GS, et al, Arch Gen Psychiatry, June 2003;60:618-626. (Address: Ingvar Bjelland, MD, E-mail: ingvar.bjelland@uib.no) 40648

ENDOTHELIAL FUNCTION - Homocysteine, Vitamin - In a study of 20 hyperhomocysteinemic men who were ≥ 40 years of age (total homocysteine > 15 $\mu\text{mol/l}$) compared with 20 age-matched controls with total homocysteine levels < 13 $\mu\text{mol/l}$, subjects randomly received 0.6 mg of folic acid, 0.8 mg of vitamin B12 and 2.0 mg of vitamin B6 or an identical placebo for 8 weeks in a double-blind trial. The subjects with elevated homocysteine levels had lower baseline serum levels of vitamin B12. Plasma total homocysteine levels decreased significantly in the supplemented group, but there was no improvement in endothelial-dependent function or antithrombotic function.

"Hyperhomocysteinemia and Endothelial Function in Young Subjects: Effects of Vitamin Supplementation," Hirsch S, De La Maza MP, Yanez P, et al, Clin Cardiol, 2002;25:495-501. (Address: Sandra Hirsch, E-mail: shirsch@ucc.inta.uchile.cl) 40276

FERTILITY/INFERTILITY - Oxidative Stress, Semen, Vitamin E - In a study of 54 voluntary and infertile men, 28 were supplemented with vitamin E at 400 mg/day and selenium at 225 mcg/day compared with 26 subjects receiving vitamin B at 4.5 g/day for the same duration containing vitamin B1 at 250 mg, vitamin B6 at 250 mg and vitamin B12 at 1 mg as 3 tablets, 3 times daily, for 3 months. Twenty patients returned for control analysis. Malondialdehyde levels in sperm were much less than in seminal plasma, and motility and viability were inversely correlated with semen malondialdehyde level. In contrast to vitamin B supplementation, vitamin E and selenium supplementation produced a significant decrease in malondialdehyde concentrations and an improvement in sperm motility. The results confirm the protective and beneficial effects of vitamin E and selenium on sperm quality and imply they should be used in male infertility treatment. **"Sperm Oxidative Stress and the Effect of an Oral Vitamin E and Selenium Supplement on Semen Quality in Infertile Men,"** Keskes-Ammar L, Feki-Chakroun N, Rebai T, et al, Arch Androl, 2003;49:83-94. (Address: Dr. Leila Keskes, E-mail: lkeskes@yahoo.fr) 40388A

HEADACHE - Hydroxocobalamin, Migraine - In 20 patients with a history of migraine for >1 year with 2-8 migraine attacks per month who participated in an open trial with a baseline period followed by an active treatment of 3 months of 1 mg intranasal hydroxocobalamin daily, there was a reduction in migraine attack frequency of =50% seen in 10 of 19 patients (53%). A reduction of =30% was seen in 63% of the patients. The mean attack frequency in the total population was reduced from 4.7 to 2.7 attacks per month. For responders, the migraine attack frequency was reduced from 5.2 to 1.9 attacks per month, while those who did not respond showed a nonsignificant reduction of 4.1 to 3.7. There was a reduction observed for the total duration of migraine attacks per month, the total number of migraine days per month, and the number of medication doses for acute treatment used per month. The patients used 1 mg of intranasal hydroxocobalamin daily by administering 50 ul of a 2% hydroxocobalamin aqueous solution. The hypothesized mechanism of hydroxocobalamin's action is due to its nitric oxide scavenging ability. **"Hydroxocobalamin, a Nitric Oxide Scavenger, in the Prophylaxis of Migraine: An Open, Pilot Study,"** van der Kuy P-HM, Merkus FWHM, et al, Cephalalgia, 2002;22:513-519. 40161

HERPES SIMPLEX - Vitamin B12 - This clinical experience indicates that vitamin B12 at 2,000 mcg administered subcutaneously every other day shortens the course of herpes simplex, of which the symptoms are relieved within 24-48 hours. Frequently, only 1 injection is needed. Vitamin B12 also shortens the course and reduces the symptoms and complications of herpes zoster. **"Vitamin B12 Chases Herpes Away,"** Munyan EA, Cortlandt Forum, February 2003:75. 40310

HOMOCYSTEINE - B Vitamin - In a cross-sectional survey of 324 men and 641 women between 20 and 74 years of age, age-adjusted plasma homocysteine levels were higher for men and women with the homozygous genotype for the gene mutation for the enzyme 5,10- methylenetetrahydrofolate reductase (MTHFR) compared to those who were heterozygous or had no mutation. Elevated homocysteine levels in the homozygous genotype were attenuated in those individuals with higher serum levels of vitamin B12 and folate, but not vitamin B6, and in individuals with combinations of lower folate and higher vitamin B12, and of higher folate and higher vitamin B12. This suggests that vitamin B12, as well as folate, may modify elevated homocysteine levels in individuals who are homozygous for the genotype for the MTHFR gene mutation. **"Effects of Serum B Vitamins on Elevated Plasma Homocysteine Levels Associated With the Mutation of Methylenetetrahydrofolate Reductase Gene in Japanese,"** Moriyama Y, Okamura T, et al, Atherosclerosis, 2002;164:321-328. (Address: Yuri Moriyama, MD, (FAX) 81 88 872 6324, E-mail: yuri_moriyama@ken4.pref.kochi.jp) 39817

HOMOCYSTEINE - Cirrhosis, Fatty Liver, Hepatitis - In a cross-sectional study of 323 subjects with chronic liver disease, of which 93 had hepatitis, 8 fatty liver, 168 cirrhosis and 54 orthotopic liver transplantation, compared with 25 healthy controls (mean age range 42.0-56.5 years), basal hyperhomocysteinemia was seen in all patient groups, which included 34% of the patients with hepatitis, 50% with fatty liver, 54% with cirrhosis and 52% with orthotopic liver transplantation. The mean plasma levels of folate were normal in patients with liver disease, but vitamin B12 levels were elevated in

cirrhosis and vitamin B6 was low after orthotopic liver transplantation. There were significant negative associations between total homocysteine and folic acid or vitamin B12 levels in control subjects and in patients with hepatitis and after orthotopic transplantation. With folic acid supplementation at 5 mg/day and vitamin B6 supplementation at 20 mg/day for 10 days, with testing on day 11, the area under the total homocysteine curve improved in cirrhosis at nearly unchanged basal total homocysteine concentrations. There was a significant improvement with folate and vitamin B6 supplementation on postprandial homocysteine metabolism. Hyperhomocysteinemia in conjunction with intracellular vitamin deficiency are highly prevalent in patients with liver disease and after orthotopic liver transplantation. **"Determinants of Hyperhomocysteinemia in Patients With Chronic Liver Disease and After Orthotopic Liver Transplantation,"** Bosy- Westphal A, Ruschmeyer M, et al, Am J CIN Nutr, 2003;77:1269-1277. (Address: Manfred James Muller, E-mail: mmueller@nutrfoodsc.uni- kiel.de) 40491

HOMOCYSTEINE - Diet - In a study of 37 healthy female volunteers, which included a baseline period and two 5-week diet periods (low- and high-folate diet) separated by a 3-week washout period, the mean concentrations of serum and red blood cell (RBC) folate were 11.0 nmol/l and 412 nmol/l at the end of the low-folate diet and 78% and 14% higher in response to the high-folate diet. The low- folate diet consisted of 1 serving of both vegetables and fruit per day, while the high-folate diet consisted of at least 7 servings of vegetables, berries and citrus fruit per day. The serum level of vitamin B12 remained unchanged during the intervention. The mean total plasma homocysteine level was 8.0 umol/l at the end of the low-folate diet and decreased by 13% in response to the high-folate diet. A diet high in fresh berries, citrus fruit and vegetables effectively increased serum and RBC folate levels while decreasing plasma homocysteine levels. **"Plasma Homocysteine Concentration Is Decreased by Dietary Intervention,"** Silaste M-L, Rantala M, et al, Br J Nutr, 2003;89:295-301. (Address: Dr. Marja-Leena Silaste, (FAX) +358 8 315 5348, E-mail: Marja-Leena.Silaste@oulu.fi) 40505

HOMOCYSTEINE - Smoking - In a case-control study of 750 cases of cardiovascular disease and 800 age- and sex-matched controls who were less than 60 years of age from 19 centers in 10 European countries, smoking was associated with an increased risk of vascular disease. The risk was greatly increased in the presence of elevated plasma homocysteine. Cigarette smokers with plasma homocysteine above 12 umol/l had a 12-fold increased risk of cardiovascular disease compared with nonsmokers with a normal plasma homocysteine level. In both cases and controls, current smokers had higher plasma homocysteine levels compared with never- smokers. Current smokers tended to have lower levels of folate, vitamin B6 and vitamin B12 than never-smokers. The risk of cardiovascular disease associated with smoking was not significantly altered after adjusting for levels of B-vitamins. Smokers with high plasma homocysteine levels are at a significantly greater risk of cardiovascular disease. Supplementation with vitamin B12, vitamin B6 and folate may be of benefit in smokers with high homocysteine levels. **"Smoking and Plasma Homocysteine,"** O'Callaghan P, Meleady R, et al, Eur Heart J, October 2002;23(20):1580-1586. 39928

INCONTINENCE - Vitamin B12 - In 258 men and 671 women who were followed between 1991 and 1999, it was found that some form of incontinence, whether urinary or fecal, was found in 41% of the subjects. Isolated urinary incontinence was found in 34%, double- incontinence was found in 12%, and isolated fecal incontinence was found in 4%. Serum vitamin B12 levels of 300 pg/ml or less were not predictive of either isolated urinary incontinence or isolated fecal incontinence. Double incontinence was predicted by vitamin B12 levels with an odds ratio of 2.113, cathartics/laxative use with an odds ratio of 1.902, and diuretic use with an odds ratio of 2.226. Since double incontinence may be associated with vitamin B12 levels, there is a possibility of treatment and prevention. **"Vitamin B12 Deficiency and Incontinence: Is There an Association?"** Endo JO, Chen S, Potter JF, et al, J Gerontol: Med Sci, 2002;57A(9):M583-M587. (Address: Jane F. Potter, MD, E-mail: jpotter@unmc.edu) 40120

NEURAL TUBE DEFECT - Vitamin B12 - In evaluating 157 Mexican American women with neural tube defect-affected pregnancies and 186 Mexican American women with normal pregnancies, compared with women in the highest vitamin B12 quintile, women in the lowest quintile showed a strong risk effect, with an odds ratio of 3.0, while those in the second and third quintiles showed moderate risk effects. Median serum vitamin B12 levels were much lower among the case mothers compared with the controls, with a difference of -68 pg/ml of serum vitamin B12. Low levels of serum vitamin B12, which are not normally suggestive of classical vitamin B12 deficiencies and do not come from an inadequate diet, may be an important etiology factor in neural tube defects along with folate levels. This study found that vitamin B12 status may be a more important etiologic factor than folate levels. **"Maternal Serum B12 Levels and Risk for Neural Tube Defects in a Texas-Mexico Border Population,"** Suarez L, Hendricks K, et al, Ann Epidemiol, February 2003;13(2):81-88. (Address: Lucina Suarez, PhD, E-mail: lucina.suarez@tdh.state.tx.us) 40321

INFECTION - Mineral, Multivitamin - In a study of 130 community- dwelling adults who were between 45 and 64 years of age or ≥65 years of age, 80 subjects (66% female) received placebo, while 78 subjects (77% female) received a multivitamin/mineral supplement daily for 1 year. The multivitamin/mineral supplement contained vitamin A at 4,000 IU, beta-carotene at 1,000 IU, vitamin B1 at 4.5 mg, vitamin B2 at 3.4 mg, vitamin B3 at 20 mg, vitamin B6 at 6 mg, vitamin B12 at 30 mcg, vitamin C at 120 mg, vitamin D at 400 IU, vitamin E at 60 IU, vitamin K at 20 mcg, biotin at 0.03 mg, pantothenic acid at 15 mg, folic acid at 400 mcg, calcium at 120 mg, magnesium at 100 mg, manganese at 4 mg, copper at 2 mg, iron at 16 mg, zinc at 22.5 mg, iodine at 150 mcg, selenium at 105 mcg and chromium at 180 mcg. More of the subjects receiving placebo reported an infectious illness over the 1-year study compared with those receiving the multivitamin/mineral supplements (73% vs 43%, respectively). Infection-related absenteeism was greater in the placebo group than in the treatment group at 57% vs 21%, respectively. In the 51 diabetic participants, it was found that 93% of the diabetic subjects who received placebo reported infection compared with 17% of those receiving the supplements. **"Effect of a Multivitamin and Mineral Supplement on Infection and Quality of Life: A Randomized, Double-Blind, Placebo-Controlled Trial,"** Barringer TA, Kirk JK, Santaniello AC, et al, Ann Intern Med, March 4,

2003;138(5):365-371. (Address: Thomas A. Barringer, MD, E-mail: tbarringer@carolinas.org) 40329

NEUROPSYCHIATRIC DISORDER - Cobalamin, Methylmalonic Acid - In evaluating 17 patients with psychosis, 28 with depression, 16 with dementia and 47 healthy controls who were between 58 and 94 years of age, mean urinary methylmalonic acid and cobalamin levels were 11.49 mmol/mol creatinine, and 231 pg/ml in psychosis and depression groups, and 6.04 mmol/mol creatinine and 308 pg/ml in the control group, respectively. Those in the dementia group had 11.53 mmol/mol creatinine and 231 pg/ml for urinary methylmalonic acid and serum cobalamin, respectively, while the control group had 6.05 mmol/mol creatinine and 364 pg/ml, respectively. There was good correlation between urinary methylmalonic acid and serum vitamin B12 levels for all groups. The correlation between urinary methylmalonic acid and red cell folate was also significant for depression, psychosis and control groups, and for the dementia group. Photometric urinary methylmalonic acid analysis should be the first diagnostic test used when cobalamin deficiency is evaluated. If the urinary methylmalonic acid is above the reference range, serum cobalamin levels may be evaluated for further diagnosis. **"Urine Methylmalonic Acid Measurements for the Assessment of Cobalamin Deficiency Related to Neuropsychiatric Disorders,"** Gultepe M, Ozcan O, et al, Clin Biochem, 2003;36:275- 282. (Address: Mustafa Gultepe, E-mail: mustafagultepe@yahoo.com) 40718

PREMATURITY - Homocysteine, Vitamin B - In this case-control study of women who were between 21 and 34 years of age, there were 29 preterm delivered living infants at <37 weeks' gestation, and 405 term controls who were delivered at =37 weeks. There were 33 cases of low-birth-weight infants weighing <2,500 g, and there 390 normal-birth-weight controls with infants weighing =2,500 g. There were 65 cases of small-for-gestational age infants below the tenth percentile of weight-for-gestational age, and there were 358 who were appropriate for their gestational age who served as controls. Elevated homocysteine levels (=12.4 umol/l) in the pregnant women were associated with a nearly 4-fold higher risk of preterm birth. The risk of preterm birth was 60% lower among women with vitamin B12 levels =258 pmol/l compared with those who were vitamin B12 deficient. The risk of preterm birth was 50% lower among women with vitamin B6 levels =30 nmol/l compared with those who were vitamin B6 deficient. There was no association between folate status and preterm birth. Homocysteine and B-vitamin status were not associated with low-birth-weight or small-for-gestational age status.

"Preconception Homocysteine and B Vitamin Status and Birth Outcomes in Chinese Women," Ronnenberg AG, Goldman MB, Chen D, et al, Am J Clin Nutr, 2002;76:1385-1391. (Address: A. G. Ronnenberg, E-mail: ronnenberg@attbi.com) 40074

STROKE - Folic Acid, Homocysteine, Vitamin B12 - Sixty-three patients with ischemic stroke received 1,500 mcg/day of oral mecobalamin, 64 received 5 mg/day of folic acid, another 64 received both mecobalamin and folic acid, and 64 acted as controls (mean ages 65.6, 64.1, 65.8, and 65.8 years, respectively). There were significant reductions in plasma homocysteine seen in all 3 groups, and the combination therapy resulted in the most remarkable reduction of plasma homocysteine by 38.5%. This was significantly

larger than the reduction in the other 2 groups at 22.4% and 10.9% in those who received the folic acid and vitamin B12, respectively. This combined therapy of folic acid and vitamin B12 may be a beneficial secondary prevention in individuals who have suffered ischemic stroke. **"Hyperhomocysteinemia in Japanese Patients With Convalescent Stage Ischemic Stroke: Effect of Combined Therapy With Folic Acid and Mecobalamine,"** Sato Y, Kaji M, et al, J Neurol Sci, 2002;202:65-68. (Address: Yoshihiro Sato, (FAX) +81-172-36-3827, E-mail: noukenrs@cc.hirosaki-u.ac.jp) 40088

VEGETARIAN - Holotranscobalamin II, Homocysteine, Methylmalonic Acid, Vitamin B12 - In a study of 79 omnivores (mean age 51 years, 56% female) compared with 66 lactoovovegetarians or lactovegetarians (mean age 48 years, 55% female) and 29 vegans (mean age 37 years, 55% female), vegans had the lowest vitamin B12 status. In those who did not consume vitamins, low holotranscobalamin II (<35 pmol/l) was found in 11% of the omnivores, 77% of the lactoovovegetarian/lactovegetarian group and 92% of the vegans. Elevated methylmalonic acid (>271 nmol/l) was found in 5% of the omnivores, 68% of the lactoovovegetarian/ lactovegetarian group and 83% of the vegans. Elevated homocysteine (>12 umol/l) was present in 16% of the omnivores, 38% of the lactoovovegetarian/lactovegetarians and 67% of the vegans. The relationship between holotranscobalamin II and vitamin B12 was weak in the low serum vitamin B12 range and strong in the high serum vitamin B12 range. Holotranscobalamin II levels were the main determinant of total homocysteine levels in the vegetarians. Vitamin B12 deficiency led to hyperhomocysteinemia that was not likely to occur in the upper folate range of >42 nmol/l. As a group, vegans and, to a lesser degree, lactoovovegetarian/ lactovegetarians had metabolic abnormalities that suggested vitamin B12 deficiency, which led to a significant increase in total homocysteine levels. Holotranscobalamin II levels, along with homocysteine and methylmalonic acid levels, may be sensitive and reliable markers in individuals who are prone to vitamin B12 deficiency. **"Vitamin B-12 Status, Particularly Holotranscobalamin II and Methylmalonic Acid Concentrations, and Hyperhomocysteinemia in Vegetarians,"** Herrmann W, Schoor H, et al, Am J Clin Nutr, 2003;78:131-136. (Address: Wolfgang Herrmann, E-mail: kchwhe@uniklinik-saarland.de) 40664

VEGETARIAN - Homocysteine, Methylmalonic Acid, Vitamin B12 - In studying 29 vegans, and 64 lacto- and lacto-ovo-vegetarians, in addition to 20 occasional meat-eaters, for a total of 49 males and 64 females (mean age 46 years), vegans showed the highest methylmalonic acid and homocysteine levels at 708 nmol/l and 12.8 umol/l, respectively, and lower lymphocyte counts and higher mean corpuscular volumes (MCV) compared with lacto- or lacto-ovo- vegetarians. Vitamin B12-deficient individuals in the higher range of transferrin saturation percentage had higher MCV than vitamin B12-deficient subjects in the lower transferrin saturation range. A lower platelet count was found in the highest quartile of methylmalonic acid and in the highest quartile of homocysteine compared with the other quartiles. Lower lymphocyte and platelet counts and higher MCV were found in subjects with elevated methylmalonic acid and homocysteine compared with those with normal metabolites. This study showed that vitamin B12 and iron status were compromised in those who consumed a vegetarian diet. **"The Impact of Vegetarianism on Some Haematological Parameters,"** Obeid R, Geisel J, et al, Eur J

Haematol, 2002;69:275-279. (Address: Prof. Dr. Wolfgang Herrmann, E-mail: kchwher@uniklinik-saarland.de) 40151

VEGETARIAN - Vitamin B12 - Stages I and II of vitamin B12 deficiency in vegetarians can be documented by a low plasma level of holotranscobalamin II, when the plasma and cell stores become depleted. Stage III is characterized by increased levels of homocysteine and methylmalonic acid in addition to lowered holotranscobalamin II. In stage IV, clinical signs become recognizable such as macroovalocytosis, elevated mean corpuscular volume of erythrocytes or lowered hemoglobin. The authors have found stage III of vitamin B12 deficiency in over 60% of vegetarians. A serum level of vitamin B12 >156 pmol/l is normal, but only a vitamin B12 level above 360 pmol/l prevents functional vitamin deficiency with more reliability. **"Vegetarian Lifestyle and Monitoring of Vitamin B12 Status,"** Herrmann W, Geisel J, Clin Chim Acta, 2002;326:47-59. (Address: Wolfgang Herrmann, (FAX) +49-6841-162-3109, E-mail: kchwher@uniklinik-saarland.de) 40098

VITAMIN - Cancer, Cardiovascular Disease - In a summary by the U.S. Preventive Services Task Force on the role of routine vitamin supplementation to prevent cancer or cardiovascular disease, results indicated that the benefits of vitamin supplementation remain uncertain, while there is more consistent evidence for a diet high in fruit, vegetables and legumes. Dietary supplementation with folic acid, vitamin B6 and vitamin B12, alone or in combination, can lower plasma homocysteine levels, and it is noted that higher levels of homocysteine are an independent risk factor for cardiovascular disease. The evidence for vitamin supplementation altering cardiovascular outcomes is lacking but may be available within the next several years. Complete information on this summary of evidence is printed in the Guide to Clinical Preventive Services, Third Edition: Periodic Updates. A subscription rate costs \$60 U.S. and can be ordered through the Agency for Healthcare Research and Quality Publications Clearinghouse at (TEL) 800-358-9295, E-mail: ahrqbubs@ahrq.gov. "Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease: Recommendations and Rationale," U.S. Preventive Services Task Force, Ann Intern Med, July 1, 2003;139(1):51-55. (Address: Agency for Healthcare Research and Quality Publications Clearinghouse, (TEL) 800-358-9295, or USPSTF, web site: www.preventiveservices.ahrq.gov) 40717

VITAMIN B12 - Aging, Deficiency - Causes of vitamin B12 deficiency include inadequate ingestion from chronic alcoholism, chronic malnutrition and strict vegetarianism; inadequate absorption due to atrophic gastritis, gastrectomy, small intestinal bacterial overgrowth, intestinal resection, malabsorption, Crohn's disease, chronic pancreatitis, and Helicobacter pylori gastritis; inadequate utilization of vitamin B12 due to medications, transcobalamin-II deficiency, and anti-vitamin B12 analogues; inadequate stores of vitamin B12 due to advanced liver disease; drug interactions relating to malabsorption due to metformin, antibiotics, phenytoin, colchicine, para-aminosalicylic acid, and cholestyramine; metabolic inactivation due to vitamin C and nitrous oxide; and food-cobalamin malabsorption due to proton pump inhibitors and H2 receptor blockers. The pathway for gastrointestinal absorption of cobalamin in the oral cavity and stomach occurs through R protein secretion by salivary glands and gastric

mucosa. In the stomach, cobalamin is separated from food by acid and peptic activity. This liberates cobalamin and binds it to R protein, forming the cobalamin-R complex. Intrinsic factor is secreted by the parietal cells. In the duodenum, the cobalamin-R complex is digested by pancreatic enzymes/alkalinity, which frees the cobalamin. The free cobalamin binds to intrinsic factor in the alkaline medium. The cobalamin- intrinsic factor moves down to the terminal ileum. In the terminal ileum, the cobalamin-intrinsic factor complex binds to specific receptors on the mucosal brush border. In the mucosal cells, the cobalamin-intrinsic factor complex bound to receptor undergoes pinocytosis. The intrinsic factor is degraded, and cobalamin is transferred to transcobalamin-II and released into the circulation as holo transcobalamin. There are two cobalamin-dependent pathways. The first pathway involves the conversion of homocysteine to methionine. The vitamin B12-dependent enzyme is methionine synthase, with the coenzyme being methylcobalamin. When there is not enough vitamin B12, there is increased homocysteine. In the second pathway, methylmalonyl CoA is converted to succinyl CoA. The enzyme for this is methylmalonyl CoA mutase, and the coenzyme is adenosylcobalamin. If there is a vitamin B12 deficiency, there is increased methylmalonic acid. Laboratory features of cobalamin deficiency include anemia, thrombocytopenia, elevated mean corpuscular volume, leukopenia, low or normal reticulocyte count, macroovalocytosis, hypersegmented neutrophils, anisocytosis, poikilocytosis, hypercellular bone marrow, increased myeloid/erythroid ratio, abundance of stainable iron in bone marrow, nuclear-cytoplasmic asynchrony, decreased megakaryocytes with abnormal morphology, reduced serum vitamin B12, increased methylmalonic acid and homocysteine, decreased holo transcobalamin- II, increased unconjugated bilirubin and increased lactate dehydrogenase enzyme. Also, false low levels of serum vitamin B12 may be due to folate deficiency, progressive multiple myeloma, use of oral contraceptive pills, multiple myeloma and excessive vitamin C intake. False normal vitamin B12 levels may occur in active liver disease, lymphoma, alcoholism, intestinal bacterial overgrowth and myeloproliferative disorders. At the age of 50, if serum cobalamin levels are >400 pg/ml, screen every 5 years. If serum vitamin B12 levels are 100-400 pg/ml, consider performing methylmalonic acid and homocysteine evaluations. If serum vitamin B12 levels are <100 pg/ml, treat for deficiency. In individuals who are ≥65 years of age, screen annually. Therapeutic options for treating vitamin B12 deficiency include intramuscular injections at 100-1,000 mcg every 1-3 months, oral intake at 500-2,000 mcg/day, sublingual forms at 2,000 mcg/day, and intranasal administration at 500 mcg weekly. **"Vitamin B12 Deficiency: Recognizing Subtle Symptoms in Older Adults,"** Dharmarajan TS, Adiga GU, Norkus EP, Geriatrics, March 2003;58(3):30-38. 40407

VITAMIN B12 - Deficiency, Homocysteine, Intrinsic Factor Antibody, Methylmalonic Acid, Parietal Cell Antibody - Vitamin B12 deficiency can cause macrocytic anemia and result in a wide variety of neuropsychiatric disorders. Vitamin B12 deficiency may be important in elevated homocysteine levels, which may increase the risk of atherosclerosis, but this needs further study. Vitamin B12 deficiency is defined as low serum vitamin B12 levels (<200 pg/ml or 150 pmol/l). Fifty-percent of patients with subclinical vitamin B12 deficiency have normal serum vitamin B12 levels. More sensitive tests for vitamin B12 deficiency include serum methylmalonic acid and

homocysteine levels, which are increased in early vitamin B12 deficiency. The use of parietal cell and intrinsic factor antibodies have replaced the Schilling test for evaluating pernicious anemia. Oral vitamin B12 is safe and effective for normalizing vitamin B12 deficiency states, even though most practitioners believe that injectable vitamin B12 is the only way to replace vitamin B12. In one study, patients with vitamin B12 deficiency who received either 1,000 mcg of vitamin B12 injections on days 1, 3, 7, 10, 14, 21, 30, 60 and 90 were compared with those who received oral supplementation at 2,000 mcg daily for 120 days. It was found that those who received oral therapy had significantly higher serum vitamin B12 levels and lower methylmalonic acid levels than those in the parenteral therapy group. Intramuscular treatment with vitamin B12 varies, but a daily injection of 1,000 mcg for 1-2 weeks and then a maintenance dose of 1,000 mcg every 1-3 months has been used. One thousand to 2,000 mcg daily for 2 weeks and then 1,000 mcg/day for life can maintain levels of vitamin B12 in those who are deficient. **"Vitamin B12 Deficiency,"** Oh RC, Brown DL, Am Fam Physician, March 1, 2003;67(5):979-986, 993-994. 40364

VITAMIN B12 - Methylmalonic Acid - In studying 1,145 elderly subjects who were ≥ 65 years of age compared with 1,026 young adult subjects who were between 30 and 39 years of age, approximately 20% of participants who were ≥ 65 years of age had serum methylmalonic acid levels >370 nmol/l. Serum methylmalonic acid levels showed a strong inverse relationship to serum vitamin B12 levels. Elevated serum methylmalonic acid levels affected approximately 15% of those with both normal serum creatinine concentrations and serum vitamin B12 concentrations >148 pmol/l. The authors note that many elderly Americans show metabolic evidence of low vitamin B12 levels, which occur frequently in the absence of traditional deficiency signs and symptoms. **"Elevated Serum Methylmalonic Acid Concentrations Are Common Among Elderly Americans,"** Morris MS, Jacques PF, et al, J Nutr, 2002;132:2799-2803. 40021

VITAMIN B12 - Vegetarian - Vegetarians are at risk for deficiency of vitamin B12. In stages I and II of vitamin B12 deficiency, there is a low plasma level of holotranscobalamin II. The plasma and cell stores become depleted of holotranscobalamin II. In stage III, there are increased levels of homocysteine and methylmalonic acid in addition to the lower levels of holotranscobalamin II. In stage IV, clinical signs develop, such as macroovalocytosis, elevated mean corpuscular volume and lowered hemoglobin. Vitamin B12 deficiency results in lower S-adenosyl-methionine, which is the universal donor of methyl groups. This can result in hypomethylation of DNA, RNA, proteins, myelin or neurotransmitters. The development of psychiatric and neurological disorders may occur, such as cognitive dysfunction, dementia or Alzheimer's disease. Optimal monitoring of vitamin B12 levels in vegetarians should include homocysteine, methylmalonic acid and holotranscobalamin II. Levels of vitamin B6 and folate should be evaluated as well. If holotranscobalamin II levels are not available, then vitamin B12 levels should be taken. Plasma homocysteine levels should be <10 μ mol/l, holotranscobalamin II levels should be >45 pmol/l and methylmalonic acid should be <271 nmol/l. Vitamin B12 levels should be above 360 pmol/l, which prevents functional vitamin B12 deficiency with more reliability. **"Vegetarian Lifestyle and Monitoring of Vitamin B-12 Status,"** Herrmann W, Geisel J, Clin Chim Acta,

2002;326:47-59. (Address: Wolfgang Herrmann, (FAX) +49-6841-162-3109, E-mail: kchwher@uniklinik-saarland.de) 40376