

## 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: garciaaa@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@ctsuo.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](mailto: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  $\geq 15$   $\mu\text{mol/l}$  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](mailto:ingvar.bjelland@uib.no)) 40648

ENDOTHELIAL FUNCTION - Homocysteine, Vitamin - In a study of 20 hyperhomocysteinemic men who were  $\geq 40$  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](mailto: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](mailto:lkeskes@yahoo.fr)) 40388A