

Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*Helicobacter pylori* therapy.

Correa P, Fontham ET, Bravo JC, et al. *J Natl Cancer Inst* 2000;92:1881-1888.

BACKGROUND: Previous research has identified a high risk of gastric carcinoma as well as a high prevalence of cancer precursor lesions in rural populations living in the province of Narino, Colombia, in the Andes Mountains. **METHODS:** A randomized, controlled chemoprevention trial was conducted in subjects with confirmed histologic diagnoses of multifocal nonmetaplastic atrophy and/or intestinal metaplasia, two precancerous lesions. Individuals were assigned to receive anti-*Helicobacter pylori* triple therapy and/or dietary supplementation with ascorbic acid, beta-carotene, or their corresponding placebos. Gastric biopsy specimens taken at baseline were compared with those taken at 72 months. Relative risks of progression, no change, and regression from multifocal nonmetaplastic atrophy and intestinal metaplasia were analyzed with multivariate polytomous logistic regression models to estimate treatment effects. All statistical tests were two-sided. **RESULTS:** All three basic interventions resulted in statistically significant increases in the rates of regression: Relative risks were 4.8 (95% confidence interval [CI] = 1.6-14.2) for anti-*H. pylori* treatment, 5.1 (95% CI = 1.7-15.0) for beta-carotene treatment, and 5.0 (95% CI = 1.7-14.4) for ascorbic acid treatment in subjects with atrophy. Corresponding relative risks of regression in subjects with intestinal metaplasia were 3.1 (95% CI = 1.0-9.3), 3.4 (95% CI = 1.1-9.8), and 3.3 (95% CI = 1.1-9.5). Combinations of treatments did not statistically significantly increase the regression rates. Curing the *H. pylori* infection (which occurred in 74% of the treated subjects) produced a marked and statistically significant increase in the rate of regression of the precursor lesions (relative risks = 8.7 [95% CI = 2.7-28.2] for subjects with atrophy and 5.4 [95% CI = 1.7-17.6] for subjects with intestinal metaplasia). **CONCLUSIONS:** In the very high-risk population studied, effective anti-*H. pylori* treatment and dietary supplementation with antioxidant micronutrients may interfere with the precancerous process, mostly by increasing the rate of regression of cancer precursor lesions, and may be an effective strategy to prevent gastric carcinoma.

Herbal-drug therapy interactions: A focus on dementia.

Gold JL, Laxer DA, Dergal JM, et al. *Curr Opin Clin Nutr Metab Care* 2001;4:29-34.

Older people with dementia are often prescribed numerous medications. Use of herbal therapies in addition to these conventional drug therapies may lead to interactions that result in an adverse drug event. We have conducted a systematic review to identify all studies that examined interactions between herbal and conventional drug therapies (i.e. prescription or over-the-counter). Using a MEDLINE search of English-language studies published between 1980 and 2000, we limited our search to those herbal therapies most likely to be used for the treatment of dementia (memory loss and decreased concentration) and related symptoms. We identified 28 articles that describe interactions between these herbal (i.e. St. John's wort, ginkgo biloba, kava, valerian, and ginseng) and conventional drug therapies. Of these articles, 11 examined St. John's wort, four examined ginkgo biloba, five examined kava, one examined valerian, and seven examined ginseng. We identified a series of potential interactions between herbal and conventional drug therapy that place older people at risk for an adverse drug event. Health care professionals need to be aware of these potential interactions.

Thiamine supplementation to prevent induction of low birth weight by conventional therapy for gestational diabetes mellitus.

Bakker SJ, ter Maaten JC, Gans RO. *Med Hypotheses* 2000;55:88-90.

Conventional treatment for gestational diabetes mellitus increases the proportion of infants born with a low birth weight, a risk factor for cardiovascular disease and diabetes mellitus in later life. Thiamine supplementation during pregnancy may be shown to be a safe preventive measure. During pregnancy, approximately 50% of the women develop a biochemical thiamine deficiency, whereas the thiamine status falls, but remains within normal limits, in most other women. Thiamine is essential for glucose oxidation, insulin production by pancreatic beta-cells and cell growth. It is therefore likely that thiamine supplementation in pregnant women not only improves their glucose tolerance but also stimulates the intra-uterine growth, thereby preventing a low birth weight to ensue from conventional therapy which only improves glucose tolerance.

Abstracts

Recently Published Abstracts

Role of sodium channel inhibition in neuroprotection: effect of vinpocetine.

Bonoczka P, Gulyas B, Adam-Vizi V, et al. *Brain Res Bull* 2000;53:245-254.

Vinpocetine (ethyl apovincaminic acid) discovered during the late 1960s has successfully been used in the treatment of central nervous system disorders of cerebrovascular origin for decades. The increase in the regional cerebral blood flow in response to vinpocetine administration is well established and strengthened by new diagnostic techniques (transcranial Doppler, near infrared spectroscopy, positron emission tomography). The latest in vitro studies have revealed the effect of the compound on Ca²⁺/calmodulin dependent cyclic guanosine monophosphate-phosphodiesterase 1, voltage-operated Ca²⁺ channels, glutamate receptors and voltage dependent Na⁺-channels; the latest being especially relevant to the neuroprotective action of vinpocetine. The good brain penetration profile and heterogeneous brain distribution pattern (mainly in the thalamus, basal ganglia and visual cortex) of labelled vinpocetin were demonstrated by positron emission tomography in primates and man. Multicentric, randomized, placebo-controlled clinical studies proved the efficacy of orally administered vinpocetin in patients with organic psychosyndrome. Recently positron emission tomography studies have proved that vinpocetine is able to redistribute regional cerebral blood flow and enhance glucose supply of brain tissue in ischemic post-stroke patients.

Interaction of *Hypericum perforatum* (St. John's wort) with cyclosporin A metabolism in a patient after liver transplantation.

Karlioiva M, Treichel U, Malago M, et al. *J Hepatol* 2000;33:853-855.

Immunosuppressive therapy in patients after liver transplantation requires careful monitoring of blood levels for immunosuppressive agents such as cyclosporin A. A variety of drugs are capable of interfering with the metabolism of cyclosporin A. We observed a 63-year-old patient who received a liver allograft for cryptogenic liver cirrhosis in 1998. This patient developed severe acute rejection 14 months after transplantation which was associated with a sudden drop in cyclosporin A levels. Two weeks previously, he had started taking the herbal drug *Hypericum perforatum* (2 x 900 mg/day) for increasing episodes of depression. The cyclosporin A dosage later had to be doubled, which caused some side effects. Finally, an assessment of oral cyclosporin A resorption suggested an enhanced cyclosporin A metabolism. *Hypericum perforatum* was stopped. Both cyclosporin A dosage and blood levels immediately returned to normal. The liver function recovered completely. In conclusion, this observation is a previously undescribed drug interaction of a widely used herbal drug (*Hypericum perforatum*, i.e. St. John's wort) in a patient after liver transplantation.

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The effect of isolated soy protein on plasma biomarkers in elderly men with elevated serum prostate specific antigen.

Urban D, Irwin W, Kirk M, et al. *J Urol* 2001;165:294-300.

PURPOSE: We performed a randomized double-blind crossover pilot study in elderly men with elevated prostate specific antigen (PSA) on the effects of the daily consumption of 2 soy beverages, each containing 20 gm. of isolated soy protein, on the isoflavone concentration in blood and urine, and on the 3 serum biomarkers cholesterol, PSA and the soluble p105 component of the p185erbB-2 proto-oncogene. **MATERIALS AND METHODS:** A total of 34 men supplemented their diet by consuming 1 of 2 soy protein beverages assigned randomly twice daily for a 6-week period. In a second 6-week period they consumed the other soy protein beverage. The beverage ISP+ provided 42 mg. of genistein and 27 mg. of daidzein daily, whereas the other beverage, ISP-, provided only 2.1 and 1.3 mg. of these isoflavones daily, respectively. Blood and 24-hour urine samples were obtained before the study, at 2-week intervals during the study and 2 weeks after study completion. **RESULTS:** ISP+ and to a lesser extent ISP- substantially increased the serum concentration and urinary output of the isoflavones and their metabolites. Serum cholesterol was significantly decreased by ISP+ irrespective of the order in which the 2 soy beverages were administered and in apparent correlation with the total isoflavone concentration. There was no significant effect of the soy beverages on serum PSA and p105erbB-2 values. **CONCLUSIONS:** This study reveals that short-term exposure of elderly men with elevated serum PSA values to soy protein containing isoflavones decreases serum cholesterol but not the serum biomarkers PSA and p105erbB-2.

The effect of an ipriflavone-containing supplement on urinary N-linked telopeptide levels in postmenopausal women.

Halpner AD, Kellermann G, Ahlgrimm MJ, et al. *J Womens Health Gend Based Med* 2000;9:995-998.

Osteoporosis is a significant health concern to our aging population. We report here the results of a pilot placebo-controlled trial of a dietary supplement containing ipriflavone, calcium, and vitamin D on a urinary marker of bone breakdown in postmenopausal women. Seven postmenopausal women not currently receiving hormone replacement therapy received either an ipriflavone-containing supplement or placebo for 3 months. Urinary N-linked telopeptides, a marker of bone breakdown, declined by 29% in those receiving the supplement, whereas an increase in this marker was observed in the group receiving the placebo. No changes were observed in salivary hormone measurements. Although our sample size was small, to the best of our knowledge, this is the first report that demonstrates changes in N-linked telopeptide levels as a result of consuming an ipriflavone-containing product. Our findings confirm those of other researchers that demonstrate the usefulness of ipriflavone at slowing the progression of bone loss and suggest that measuring N-linked telopeptides may be a useful tool to assess therapeutic efficacy.

Differentiating agents in pediatric malignancies: retinoids in neuroblastoma.

Reynolds CP. *Curr Oncol Rep* 2000;2:511-518.

Retinoids are derivatives of vitamin A that include all- trans-retinoic acid (ATRA), 13-cis-retinoic acid, (13-cis-RA), and fenretinide (4-HPR). High levels of either ATRA or 13-cis-RA can cause arrest of cell growth and morphologic differentiation of human neuroblastoma cell lines. Phase I trials have shown that higher and more sustained drug levels were obtained with 13-cis-RA relative to ATRA. A phase III randomized trial showed that high-dose pulse therapy with 13-cis-RA given after completion of intensive chemoradiotherapy (with or without autologous bone marrow transplantation) significantly improves event-free survival in high-risk neuroblastoma. Because 4-HPR achieves multi-log cell kills in neuroblastoma cell lines that are resistant to ATRA and 13-cis-RA, a pediatric phase I trial is in progress to determine the maximum tolerated dose of 4-HPR, with a view toward giving 4-HPR after completion of myeloablative therapy and 13-cis-RA.

Abstracts

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Lipoic acid decreases lipid peroxidation and protein glycosylation and increases (Na(+)+K(+))- and Ca(++)-ATPase activities in high glucose-treated human erythrocytes.

Jain SK, Lim G. *Free Radic Biol Med* 2000;29:1122-1128.

Lipoic acid supplementation has been found to be beneficial in preventing neurovascular abnormalities in diabetic neuropathy. Insufficient (Na(+)+K(+))-ATPase activity has been suggested as a contributing factor in the development of diabetic neuropathy. This study was undertaken to test the hypothesis that lipoic acid reduces lipid peroxidation and glycosylation and can increase the (Na(+)+K(+))- and Ca(++)-ATPase activities in high glucose-exposed red blood cells (RBC). Washed normal human RBC were treated with normal (6 mM) and high glucose concentrations (45 mM) with 0-0.2 mM lipoic acid (mixture of S and R stereoisomers) in a shaking water bath at 37 degrees C for 24 h. There was a significant stimulation of glucose consumption by RBC in the presence of lipoic acid both in normal and high glucose-treated RBC. Lipoic acid significantly lowered the level of glycated hemoglobin (GHb) and lipid peroxidation in RBC exposed to high glucose concentrations. High glucose treatment significantly lowered the activities of (Na(+)+K(+))- and Ca(++)-ATPases of RBC membranes. Lipoic acid addition significantly blocked the reduction in activities of (Na(+)+K(+))- and Ca(++)-ATPases in high glucose-treated RBC. There were no differences in lipid peroxidation, GHb and (Na(+)+K(+))- and Ca(++)-ATPase activity levels in normal glucose-treated RBC with and without lipoic acid. Thus, lipoic acid can lower lipid peroxidation and protein glycosylation, and increase (Na(+)+K(+))- and Ca(++)-ATPase activities in high-glucose exposed RBC, which provides a potential mechanism by which lipoic acid may delay or inhibit the development of neuropathy in diabetes.

Effects of beta-carotene supplementation for six months on clinical and laboratory parameters in patients with cystic fibrosis.

Renner S, Rath R, Rust P, et al. *Thorax* 2001;56:48-52.

BACKGROUND: Patients with cystic fibrosis (CF) have significantly decreased plasma concentrations of nutrient antioxidant vitamins, especially of beta-carotene, which is thought to result from fat malabsorption and chronic pulmonary inflammation. The aim of this double blind, placebo controlled study was to investigate the effect of oral beta-carotene supplementation for six months on clinical parameters. **METHODS:** Twenty four patients with CF were randomised to receive beta-carotene 1 mg/kg/day (maximum 50 mg/day) for three months (high dose supplementation) and 10 mg/day for a further three months (low dose supplementation) or placebo. At monthly follow up visits the plasma beta-carotene concentration, total antioxidant capacity, malondialdehyde (MDA) as a marker of lipid peroxidation, and clinical parameters (Shwachmann-Kulczycki score, body mass index (BMI), height, and lung function (FEV₁)) were assessed. The number of pulmonary exacerbations requiring antibiotic treatment (in days) three months before and during the study were evaluated. **RESULTS:** The plasma concentration of beta-carotene increased significantly to the normal range during the three months of high dose supplementation (baseline 0.08 (0.04) $\mu\text{mol/l}$ to 0.56 (0.38) $\mu\text{mol/l}$; $p < 0.001$) but decreased to 0.32 (0.19) $\mu\text{mol/l}$ in the period of low dose supplementation. Initially raised plasma levels of MDA fell to normal levels and the total antioxidant capacity showed a non-significant trend towards improvement during high dose supplementation. Antibiotic treatment decreased significantly in the supplementation group from 14.5 (14.9) days/patient during the three months before the study to 9.8 (10.3) days/patient during high dose supplementation ($p = 0.0368$) and to 10.5 (9.9) days/patient during low dose supplementation, but increased in the placebo group. The Shwachmann-Kulczycki score, lung function, and BMI did not show any changes in either of the treatment groups. No adverse events were observed during the study period. **CONCLUSION:** Oral beta-carotene supplementation in a dose of 1 mg/kg/day only was effective in normalising the plasma concentration of beta-carotene and resulted in a decrease in pulmonary exacerbations. These data suggest that patients with CF may benefit clinically from supplementation with beta-carotene and further studies are warranted.

Abstracts

Recently Published Abstracts

Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin.

Abate A, Yang G, Dennery PA, et al. *Free Radic Biol Med* 2000;29:1135-1142.

The use of aspirin in rheumatoid arthritis is limited since inhibition of the pro-inflammatory enzyme cyclooxygenase-2 occurs only at higher aspirin doses that are often associated with side effects such as gastric toxicity. Using a macrophage cell line (J774. 1A), the present study explores possible synergistic effects of aspirin and vitamin E on the expression and activity of cyclooxygenase-2. Lipopolysaccharide-induced prostaglandin E(2) formation was significantly reduced by aspirin (1-100 μM) or vitamin E (100-300 μM). When combined with vitamin E, aspirin-dependent inhibition of prostaglandin E(2) formation was increased from 59% to 95% of control. Likewise, lipopolysaccharide-induced cyclooxygenase-2 protein and mRNA expression were virtually abolished by the combined treatment of aspirin and vitamin E, whereas the two agents alone were only modestly effective. Vitamin C did not mimic the actions of vitamin E under these conditions, suggesting that redox-independent mechanisms underlie the action of vitamin E. In agreement with this, vitamin E and aspirin were without effect on lipopolysaccharide-induced translocation of the redox-sensitive transcription factor NF-kappa B. Our results show that co-administration of vitamin E renders cyclooxygenase-2 more sensitive to inhibition by aspirin by as yet unknown mechanisms. Thus, anti-inflammatory therapy might be successful with lower aspirin doses when combined with vitamin E, thereby possibly avoiding the side effects of the usually required high dose aspirin treatment.

Oral glutamine in the prevention of fluorouracil induced intestinal toxicity: a double blind, placebo controlled, randomised trial.

Daniele B, Perrone F, Gallo C, et al. *Gut* 2001;48:28-33.

BACKGROUND: 5-Fluorouracil (FU) in association with folinic acid (FA) is the most frequently used chemotherapeutic agent in colorectal cancer but it often causes diarrhoea. Animal and human studies suggest that glutamine stimulates intestinal mucosal growth. **AIM:** To determine if oral glutamine prevents changes in intestinal absorption (IA) and permeability (IP) induced by FU/FA. **METHODS:** Seventy chemotherapy naive patients with colorectal cancer were randomly assigned to oral glutamine (18 g/day) or placebo before the first cycle of FU (450 mg/m²) and FA (100 mg/m²) administered intravenously for five days. Treatment was continued for 15 days, starting five days before the beginning of chemotherapy. IA (D-xylose urinary excretion) and IP (cellobiose-mannitol test) were assessed at baseline and four and five days after the end of the first cycle of chemotherapy, respectively. Patients kept a daily record of diarrhoea, scored using the classification system of the National Cancer Institute (Bethesda, Maryland, USA). Duration of diarrhoea was recorded and the area under the curve (AUC) was calculated for each patient. **RESULTS:** Baseline patient characteristics and basal values of IP and IA tests were similar in the two arms. After one cycle of chemotherapy, the reduction in IA (D-xylose absorption) was more marked in the placebo arm (7.1% v 3.8%; p=0.02); reduction of IP to mannitol was higher in the placebo arm (9.2% v 4.5%; p=0.02); and urinary recovery of cellobiose was not different between the study arms (p=0.60). Accordingly, the cellobiose-mannitol ratio increased more in the placebo arm (0.037 v 0.012; p=0.04). Average AUC of diarrhoea (1.9 v 4.5; p=0.09) and average number of loperamide tablets taken (0.4 v 2.6; p=0.002) were reduced in the glutamine arm. **CONCLUSIONS:** Glutamine reduces changes in IA and IP induced by FU and may have a protective effect on FU induced diarrhoea.

Abstracts

Recently Published Abstracts

Glycyrrhizic acid: the assessment of a no effect level.

van Gelderen CE, Bijlsma JA, van Dokkum W, Savelkoul TJ. *Hum Exp Toxicol* 2000;19:434-439.

Because from earlier experiments in rats and a pilot study in humans a no-effect level of glycyrrhizic acid could not be established, a second experiment was performed in healthy volunteers. The experiment was performed in females only, because the effects were most marked in females in the pilot study. Doses of 0, 1, 2 and 4 mg glycyrrhizic acid/kg body weight were administered orally for 8 weeks to 39 healthy female volunteers aged 19-40 years. The experiment lasted 12 weeks including an adaptation and a "wash-out" period. A no-effect level of 2 mg/kg is proposed from the results of this study, from which an acceptable daily intake (ADI) of 0.2 mg/kg body weight can be extrapolated with a safety factor of 10. This means consumption of 12 mg glycyrrhizic acid/day for a person with a body weight of 60 kg. This would be equal to 6 g licorice a day, assuming that licorice contains 0.2% of glycyrrhizic acid. The proposed ADI is below the limit advised by the Dutch Nutrition Council of 200 mg glycyrrhizic acid/day. This reflects the relatively mild acute toxicity of glycyrrhizic acid, which is also emphasised by the "generally recognised as safe" (GRAS) status of glycyrrhizic acid in the USA in 1983. However, the long-term effects of a mild chronic intoxication (causing, for example, a mild hypertension), although not immediately lethal, justify special attention to the amount of glycyrrhizic acid used daily.

Enhancing immunity by dietary consumption of a probiotic lactic acid bacterium

(*Bifidobacterium lactis* HN019): optimization and definition of cellular immune responses.

Chiang BL, Sheih YH, Wang LH, et al. *Eur J Clin Nutr* 2000;54:849-855.

Objective: To define the cellular basis for immune enhancement by a probiotic lactic acid bacteria strain (*Bifidobacterium lactis* HN019); and to determine whether immune enhancement can be optimized by delivery in oligosaccharide-enriched low-fat milk. **Design:** A double-blind, three-stage before-and-after intervention trial. **Setting:** Taipei Medical College Hospital, Taipei, Taiwan. **Subjects:** Fifty healthy Taiwanese citizens (age range 41-81; median 60) randomly allocated to two groups. **Interventions:** In stage 1 (run-in control stage) all subjects consumed reconstituted low-fat milk (LFM) for 3 weeks; in stage 2 (probiotic intervention) subjects consumed *B. lactis* in LFM (group A) or *B. lactis* in lactose-hydrolysed LFM (group B) for 3 weeks; in stage 3 all subjects returned to non-supplemented LFM for a further 3 weeks (washout stage). The innate immune functions of two different leucocyte types (polymorphonuclear (PMN) cells and natural killer (NK) cells) were assessed at four time points via in vitro analyses on peripheral blood samples. **Results:** While consumption of LFM alone had no significant effect on immune responses, stage 2 results indicated significantly enhanced PMN cell phagocytosis and NK cell tumour killing activity following consumption of milk containing *B. lactis*. These increases levelled off following cessation of *B. lactis* consumption, but remained above the pre-treatment values. Increases in PMN and NK cell activity were greatest among subjects who consumed *B. lactis* in lactose-hydrolysed LFM. **Conclusions:** Dietary consumption of the probiotic bacterium *B. lactis* HN019 enhanced immune function of two different types of leucocytes; the degree of enhancement was increased by consuming *B. lactis* in an oligosaccharide-rich substrate.

Probiotics in the management of atopic eczema.

Isolauri E, Arvola T, Sutas Y, et al. *Clin Exp Allergy* 2000;30:1605-1610.

BACKGROUND: Over the last two decades the incidence of allergic diseases has increased in industrialized countries, and consequently new approaches have to be explored. **OBJECTIVE:** The potential of probiotics to control allergic inflammation at an early age was assessed in a randomized double-blind placebo-controlled study. **METHODS:** A total of 27 infants, mean age 4.6 months, who manifested atopic eczema during exclusive breast-feeding and who have had no exposure to any infant or substitute formula were weaned to probiotic-supplemented, *Bifidobacterium lactis* Bb-12 or *Lactobacillus* strain GG (ATCC 53103), extensively hydrolysed whey formulas or to the same formula without probiotics. The extent and severity of atopic eczema, the growth and nutrition of infants, and concentrations of circulating cytokines/chemokines and soluble cell surface adhesion molecules in serum and methyl-histamine and eosinophilic protein X in urine were determined. **RESULTS:** The SCORAD score reflecting the extent and severity of atopic eczema was 16 (7-25) during breast-feeding, median (interquartile range). After 2 months, a significant improvement in skin condition occurred in patients given probiotic-supplemented formulas, as compared to the unsupplemented group; $\chi^2 = 12.27$, $P = 0.002$. SCORAD decreased in the *Bifidobacterium lactis* Bb-12 group to 0 (0-3.8), and in the *Lactobacillus* GG group to 1 (0.1-8.7), vs unsupplemented 13.4 (4.5-18.2), median (interquartile range), in parallel with a reduction in the concentration of soluble CD4 in serum and eosinophilic protein X in urine. **CONCLUSION:** The results provide the first clinical demonstration of specific probiotic strains modifying the changes related to allergic inflammation. The data further indicate that probiotics may counteract inflammatory responses beyond the intestinal milieu. The combined effects of these probiotic strains will guide infants through the weaning period, when sensitization to newly encountered antigens is initiated. The probiotic approach may thus offer a new direction in the search for future foods for allergy treatment and prevention strategies.

Homocysteine in inflammatory bowel disease: a risk factor for thromboembolic complications?

Oldenburg B, Fijnheer R, van der Griend R, et al. *Am J Gastroenterol* 2000;95:2825-2830.

OBJECTIVE: Patients with inflammatory bowel disease (IBD) are at increased risk for thromboembolic events. Hyperhomocysteinemia, which is an established risk factor for arterial as well as venous thrombosis, may be more prevalent in IBD because of vitamin deficiencies. **METHODS:** In this retrospective study, we studied the concentrations of total homocysteine (tHcy), cobalamin, folate, and pyridoxine in 231 consecutive patients with IBD, of whom 16 patients had a history of venous thrombosis, and nine a history of arterial thrombosis. Age- and gender-matched healthy volunteers served as controls (n = 102). **RESULTS:** Homocysteine concentrations in patients were higher (12.3 micromol/L [range 4.6-51.3] vs 11.1 micromol/L [range 3.9-27.6], p = 0.001) and hyperhomocysteinemia tended to be more prevalent in patients than in the controls (11.1% vs 5%, p = 0.07). Folate, cobalamin, creatinine, and pyridoxine concentrations were correlated with tHcy. Folate deficiency was infrequently encountered in IBD patients (4.3%). The tHcy concentration in patients with a history of venous or arterial thrombosis was not higher than in patients without a history of thrombosis (12.7 micromol/L [range 4.6-40.1] and 15.2 micromol/L (range 10.5-26.8) vs 12.3 micromol/L [range 10.5-26.8], not significant). Hyperhomocysteinemia was found in 18.8% of the patients with venous thrombosis, 11.1% of the patients with arterial thrombosis, and 10.5% of the patients without thrombosis (not significant). **CONCLUSIONS:** Hyperhomocysteinemia is a common phenomenon in IBD and correlates with serum folate, cobalamin, creatinine, and pyridoxine concentrations. No correlation between tHcy and a history of venous or arterial thromboembolic complications is found. Hyperhomocysteinemia does not seem to be a major contributory factor in the development of venous or arterial thrombosis in IBD patients.

Improved vascular endothelial function after oral B vitamins: An effect mediated through reduced concentrations of free plasma homocysteine.

Chambers JC, Ueland PM, Obeid OA, et al. *Circulation* 2000;102:2479-2483.

BACKGROUND: Hyperhomocysteinemia is an independent risk factor for coronary heart disease (CHD). Dietary supplementation with B vitamins lowers plasma homocysteine by up to 30%. However, little is known about the potential beneficial effects of homocysteine lowering on vascular function in patients with CHD. **Methods and Results-**We investigated 89 men with CHD (aged 56 [range 39 to 67] years). Brachial artery flow-mediated dilatation (endothelium dependent) and nitroglycerin-induced dilatation (endothelium independent) were measured before and 8 weeks after treatment with either (1) folic acid (5 mg) and vitamin B(12) (1 mg) daily (n=59) or (2) placebo (n=30). Total, protein-bound, and free plasma homocysteine, serum folate, and vitamin B(12) were measured at baseline and at 8 weeks. Flow-mediated dilatation improved after treatment with B vitamins (2.5+/-3.2% to 4.0+/-3.7%, P:=0.002) but not placebo (2.3+/-2.6% to 1.9+/-2.6%, P:=0.5). Vitamin therapy lowered plasma concentrations of total homocysteine (from 13.0+/-3.4 to 9.3+/-1.9 &mgr;mol/L, P:<0.001), protein-bound homocysteine (from 8.7+/-2.8 to 6.2+/-1.4 &mgr;mol/L, P:<0.001), and free homocysteine (from 4.3+/-1.2 to 3.0+/-0.6 &mgr;mol/L, P:<0.001) and raised concentrations of serum folate (from 10.3+/-4.3 to 31.2+/-10.8 ng/mL, P:<0.001) and vitamin B(12) (from 314+/-102 to 661+/-297 pg/mL, P:<0.001). In regression analysis, improved flow-mediated dilatation correlated closely with the reduction in free plasma homocysteine (r=-0.26, P:=0.001), independent of changes in protein-bound homocysteine, folate, and vitamin B(12). Nitroglycerin-induced dilatation was unchanged after both B vitamins and placebo. **CONCLUSIONS:-** Folic acid and vitamin B(12) supplementation improves vascular endothelial function in patients with CHD, and this effect is likely to be mediated through reduced concentrations of free plasma homocysteine concentrations. Our data support the view that lowering homocysteine, through B vitamin supplementation, may reduce cardiovascular risk.

Folic acid antagonists during pregnancy and the risk of birth defects.

Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. *N Engl J Med* 2000;343:1608-1614.

Background: Multivitamin supplementation in pregnant women may reduce the risks of cardiovascular defects, oral clefts, and urinary tract defects in their infants. We evaluated whether the folic acid component of multivitamins is responsible for the reduction in risk by examining the associations between maternal use of folic acid antagonists and these congenital malformations. **Methods:** We assessed exposure to folic acid antagonists that act as dihydrofolate reductase inhibitors and to certain antiepileptic drugs in 3870 infants with cardiovascular defects, 1962 infants with oral clefts, and 1100 infants with urinary tract defects and also in 8387 control infants with malformations the risk of which is not reduced after vitamin supplementation. Mothers were interviewed within six months after delivery about their medication use during pregnancy. **Results:** The relative risks of cardiovascular defects and oral clefts in infants whose mothers were exposed to dihydrofolate reductase inhibitors during the second or third month after the last menstrual period, as compared with infants whose mothers had no such exposure, were 3.4 (95 percent confidence interval, 1.8 to 6.4) and 2.6 (95 percent confidence interval, 1.1 to 6.1), respectively. The relative risks of cardiovascular defects, oral clefts, and urinary tract defects after maternal exposure to antiepileptic drugs were 2.2 (95 percent confidence interval, 1.4 to 3.5), 2.5 (95 percent confidence interval, 1.5 to 4.2), and 2.5 (95 percent confidence interval, 1.2 to 5.0), respectively. Use of multivitamin supplements containing folic acid diminished the adverse effects of dihydrofolate reductase inhibitors, but not that of antiepileptic drugs. **Conclusions:** Folic acid antagonists, which include such common drugs as trimethoprim, triamterene, carbamazepine, phenytoin, phenobarbital, and primidone, may increase the risk not only of neural-tube defects, but also of cardiovascular defects, oral clefts, and urinary tract defects. The folic acid component of multivitamins may reduce the risks of these defects.

Effects of long-term supplementation with moderate pharmacologic doses of vitamin E are saturable and reversible in patients with type 1 diabetes.

Engelen W, Keenoy BM, Vertommen J, De Leeuw I.
Am J Clin Nutr
2000;72:1142-1149.

BACKGROUND: Vitamin E supplementation has been proposed as adjunctive therapy to counteract the increased LDL oxidation in diabetes and thus prevent or delay cardiovascular complications. **OBJECTIVE:** The objective of this study was to investigate the effect of a moderate pharmacologic dose of vitamin E for $</=1$ y in patients with type 1 diabetes. **DESIGN:** The study was double blind and the subjects were randomly assigned to 2 groups: the supplemented group (group S; n = 22) received 250 IU (168 mg) RRR-alpha-tocopherol 3 times/d for 1 y and the placebo group (group P; n = 22) received a placebo for 6 mo followed by 250 IU (168 mg) RRR-alpha-tocopherol 3 times/d for an additional 6 mo. **RESULTS:** Serum vitamin E doubled after 3 mo of supplementation, from a mean (+/-SD) of 36.9 +/- 10.9 to 66.4 +/- 18.3 $\mu\text{mol/L}$ (P: < 0.0005). Although lipid profiles, glycated hemoglobin, and blood biochemistry values did not change significantly, copper-induced in vitro peroxidizability of LDL and VLDL decreased after 3 mo of supplementation: the production of thiobarbituric acid-reactive substances decreased by 30-60% (P: < 0.005) and the lag time for the appearance of fluorescent products increased from 107 +/- 25 to 123 +/- 30 min in group S (P: = 0.002 compared with group P). Vitamin E supplementation for an additional 3-9 mo resulted in no further changes in serum vitamin E and lipoprotein peroxidizability. Values returned to baseline after supplementation ended. **CONCLUSIONS:** Because the improvement in lipoprotein peroxidizability is saturable and reversible, life-long supplementation with vitamin E should be considered in patients with type 1 diabetes.

Interactions between N-acetylcysteine and ascorbic acid in modulating mutagenesis and carcinogenesis.

D'Agostini F, Balansky RM, Camoirano A, De Flora S.
Int J Cancer 2000;88:702-707.

Both ascorbic acid (AsA, vitamin C) and N-acetylcysteine (NAC), a precursor and analogue of glutathione, possess a broad array of biological properties underlying their protective role in a variety of pathophysiological conditions. However, under certain circumstances, AsA behaves as a pro-oxidant rather than an antioxidant and produces adverse effects. This prompted us to evaluate whether NAC could interact with AsA in preventing mutation and cancer. AsA significantly increased spontaneous revertants in the *Salmonella typhimurium* strains TA102 and TA104, which are sensitive to oxidative mutagens. In contrast, NAC lowered the spontaneous background in TA104 and neutralized the negative effects of AsA. Moreover, NAC and AsA showed additive effects in reducing chromium(VI) and in reverting its mutagenicity. A single i.p. injection of urethane (1 g/kg body weight) to 120 A/J mice resulted, after 4 months, in the formation of a total of 1,532 lung tumors, 425 in the 30 mice treated with the carcinogen only, 404 in those treated with urethane plus AsA, 365 in those treated with urethane plus NAC and 338 in those treated with urethane plus the combination of AsA and NAC (both given daily with drinking water at the dose of 1 g/kg body weight). Compared to positive controls, tumor multiplicity was poorly affected by AsA, whereas it was significantly decreased by NAC and even more so by its combination with AsA. The overall volumes of lung tumors in the 4 groups were 107.5, 89.3, 61.3 and 49.7 mm³, respectively. Tumor sizes were slightly but significantly decreased in mice treated with AsA and more so in those treated with NAC and NAC plus AsA, their combination being significantly more effective than each individually. All protective effects elicited by combining the 2 drugs were additive. Therefore, NAC prevents the adverse effects of AsA on spontaneous mutagenicity; at the same time, this thiol behaves in an additive fashion with AsA, inhibiting the mutagenicity of chromium(VI) and the lung tumorigenicity of urethane in mice. These findings suggest that NAC and AsA could conveniently be combined in cancer chemoprevention and other pharmacological interventions.

Gamma-tocopherol partially protects insulin-secreting cells against functional inhibition by nitric oxide.

Sjoholm A, Berggren PO, Cooney RV. *Biochem Biophys Res Commun* 2000;277:334-340.

Preceding the onset of type 1 diabetes mellitus, pancreatic islets are infiltrated by macrophages secreting interleukin-1beta (IL-1beta) which induces beta-cell apoptosis and exerts inhibitory actions on islet beta-cell insulin secretion. IL-1beta seems to act chiefly through induction of nitric oxide (NO) synthesis. Hence, IL-1beta and NO have been implicated as key effector molecules in type 1 diabetes mellitus. In this paper, the influence of endogenously produced and exogenously delivered NO on the regulation of cell proliferation, cell viability and discrete parts of the stimulus-secretion coupling in insulin-secreting RINm5F cells was investigated. Because vitamin E may delay diabetes onset in animal models, we also investigated whether tocopherols may protect beta-cells from the suppressive actions of IL-1 and NO in vitro. To this end, the impact of NO on insulin secretory responses to activation of phospholipase C (by carbamylcholine), protein kinase C (by phorbol ester), adenylyl cyclase (by forskolin), and Ca(2+) influx through voltage-activated Ca(2+) channels (by K(+)-induced depolarization) was monitored in culture after treatment with IL-1beta or by co-incubation with the NO donor spermine-NONOate. It was found that cell proliferation, viability, insulin production and the stimulation of insulin release evoked by carbamylcholine and phorbol ester were impeded by IL-1beta or spermine-NONOate, whereas the hormone output by the other secretagogues was not altered by NO. Pretreatment with gamma-tocopherol (but not alpha-tocopherol) afforded a partial protection against the inhibitory effects of NO, whereas specifically inhibiting inducible NO synthase with N-nitro-L-arginine completely reversed the IL-1beta effects. In contrast, inhibiting guanylyl cyclase with ODQ (1H-[1,2, 4]oxadiazolo[4,3-alpha]-quinoxaline-1-one) or blocking low voltage-activated Ca(2+) channels with NiCl(2) failed to influence the actions of NO. In conclusion, our data show that NO inhibits growth and insulin secretion in RINm5F cells, and that gamma-tocopherol may partially prevent this. The results suggest that phospholipase C or protein kinase C may be targeted by NO. In contrast, cGMP or low voltage-activated Ca(2+) channels appear not to mediate the toxicity of NO in these cells. These adverse effects of NO on the beta-cell, and the protection by gamma-tocopherol, may be of importance for the development of the impaired insulin secretion characterizing type 1 diabetes mellitus, and offer possibilities for intervention in this process.

Alpha tocopherol supplementation decreases serum C-reactive protein and monocyte interleukin-6 levels in normal volunteers and type 2 diabetic patients.

Devaraj S, Jialal I. *Free Radic Biol Med* 2000;29:790-792.

Type 2 diabetic subjects have an increased propensity to premature atherosclerosis. Alpha tocopherol (AT), a potent antioxidant, has several anti-atherogenic effects. There is scanty data on AT supplementation on inflammation in Type 2 diabetic subjects. The aim of the study was to test the effect of RRR-AT supplementation (1200 IU/d) on plasma C-reactive protein (CRP) and interleukin-6 (IL-6) release from activated monocyte in Type 2 diabetic patients with and without macrovascular complications compared to matched controls. The volunteers comprised Type 2 diabetic subjects with macrovascular disease (DM2-MV, n = 23), Type 2 diabetic subjects without macrovascular complications (DM2, n = 24), and matched controls (C, n = 25). Plasma high sensitive CRP (Hs-CRP) and Monocyte IL-6 were assayed at baseline, following 3 months of supplementation and following a 2 month washout phase. DM2-MV subjects have elevated HsCRP and monocyte IL-6 compared to controls. AT supplementation significantly lowered levels of C-reactive protein and monocyte interleukin-6 in all three groups. In conclusion, AT therapy decreases inflammation in diabetic patients and controls and could be an adjunctive therapy in the prevention of atherosclerosis.

The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: new results of a randomized clinical trial.

van Dongen MC, van Rossum E, Kessels AG, et al.
J Am Geriatr Soc
2000;48:1183-1194.

OBJECTIVES: To evaluate the efficacy, the dose-dependence, and the durability of the effect of the ginkgo biloba special extract EGb 761 (ginkgo) in older people with dementia or age-associated memory impairment. **DESIGN:** A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial. **SETTING:** Homes for the elderly in the southern part of the Netherlands. **PARTICIPANTS:** Older persons with dementia (either Alzheimer's dementia or vascular dementia; mild to moderate degree) or age-associated memory impairment (AAMI). 214 Participants were recruited from 39 homes for the elderly. **INTERVENTION:** The participants were allocated randomly to treatment with EGb 761 (2 tablets per day, total dosage either 240 (high dose) or 160 (usual dose) mg/day) or placebo (0 mg/d). The total intervention period was 24 weeks. After 12 weeks of treatment, the initial ginkgo users were randomized once again to either continued ginkgo treatment or placebo treatment. Initial placebo use was prolonged after 12 weeks. **MEASUREMENTS:** Outcomes were assessed after 12 and 24 weeks of intervention. Outcome measures included neuropsychological testing (trail-making speed (NAI-ZVT-G), digit memory span (NAI-ZN-G), and verbal learning (NAI-WL)), clinical assessment (presence and severity of geriatric symptoms (SCAG), depressive mood (GDS), self-perceived health and memory status (report marks)), and behavioral assessment (self-reported level of instrumental daily life activities). **RESULTS:** An intention-to-treat analysis showed no effect on each of the outcome measures for participants who were assigned to ginkgo (n = 79) compared with placebo (n = 44) for the entire 24-week period. After 12 weeks of treatment, the combined high dose and usual dose ginkgo groups (n = 166) performed slightly better with regard to self-reported activities of daily life but slightly worse with regard to self-perceived health status compared with the placebo group (n = 48). No beneficial effects of a higher dose or a prolonged duration of ginkgo treatment were found. We could not detect any subgroup that benefited from ginkgo. Ginkgo use was also not associated with the occurrence of (serious) adverse events. **CONCLUSIONS:** The results of our trial suggest that ginkgo is not effective as a treatment for older people with mild to moderate dementia or age-associated memory impairment. Our results contrast sharply with those of previous ginkgo trials.

Virological and immunological effects of antioxidant treatment in patients with HIV infection.

Muller F, Svardal AM, Nordoy I, et al. *Eur J Clin Invest* 2000;30:905-914.

BACKGROUND: Intracellular oxidative stress in CD4+ lymphocytes due to disturbed glutathione homeostasis may lead to impaired lymphocyte functions and enhanced HIV replication in patients with HIV infection, especially in those with advanced immunodeficiency. The aim of the present study was to assess whether short-term, high-dose antioxidant treatment might have effects on immunological and virological parameters in patients with HIV infection. **MATERIALS AND METHODS:** In this pilot study, we examined virological and immunological effects of antioxidant combination treatment for 6 days with high doses of N-acetylcysteine (NAC) and vitamin C in 8 patients with HIV infection. The following were assayed before, during and after antioxidant treatment: HIV RNA plasma levels; numbers of CD4+, CD8+, and CD14+ leukocytes in blood; plasma thiols; intracellular glutathione redox status in CD4+ lymphocytes and CD14+ monocytes; lymphocyte proliferation; lymphocyte apoptosis and plasma levels of tumour necrosis factor (TNF)alpha; soluble TNF receptors and neopterin in plasma. **RESULTS:** No significant changes in HIV RNA plasma levels or CD4+ lymphocyte counts in blood were noted during antioxidant treatment in the patient group. However, in the 5 patients with the most advanced immunodeficiency (CD4+ lymphocyte counts < 200 x 10⁶ L⁻¹), a significant rise in CD4+ lymphocyte count, a reduction in HIV RNA plasma level of 0.8 log, an enhanced lymphocyte proliferation and an increased level of intracellular glutathione in CD4+ lymphocytes were found. No change in lymphocyte apoptosis was noted. **CONCLUSIONS:** Short-term, high-dose combination treatment with NAC and vitamin C in patients with HIV infection and advanced immunodeficiency lead to immunological and virological effects that might be of therapeutic value.

Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials.

Pittler MH, Ernst E. *Am J Med* 2000;108:276-281.

PURPOSE: The optimal treatment of intermittent claudication has not yet been identified. Ginkgo biloba extract has been reported to have beneficial effects. We performed a meta-analysis of the efficacy of Ginkgo biloba extract for intermittent claudication based on the results of randomized, placebo-controlled, double-blind trials. **METHODS:** Literature searches of MEDLINE, EMBASE, BIOSIS, AMED, CISCOP, and the Cochrane Library were performed to identify studies on the topic. Manufacturers of commercial Ginkgo biloba products and authors of original publications and reviews were contacted to provide additional information. No language restrictions were imposed. **RESULTS:** Eight randomized, placebo-controlled, double-blind trials were included. Meta-analysis found a significant difference in the increase in pain-free walking distance in favor of Ginkgo biloba (weighted mean difference: 34 meters, 95% confidence interval [CI]: 26 to 43 meters). In studies using similar methodological features (ergometer speed: 3 km/h, inclination: 12%) this difference was 33 meters in favor of Ginkgo biloba (95% CI: 22 to 43 meters). Adverse effects were rare, mild, and transient. **CONCLUSIONS:** These results suggest that Ginkgo biloba extract is superior to placebo in the symptomatic treatment of intermittent claudication. However, the size of the overall treatment effect is modest and of uncertain clinical relevance.