

Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies.

Tapiero H, Ba GN, Couvreur P, Tew KD. *Biomed Pharmacother* 2002;56:215-222.

Linoleic and alpha-linolenic acids, obtained from plant material in the diet are the precursors in tissues of two families with opposing effects which are referred to as "essential fatty acids" (EFA): arachidonic acid (AA) and pentaene (eicosapentaenoic acid: EPA) and hexaene (docosahexaenoic acid: DHA) acids. The role of EFA is crucial, without a source of AA or compounds which can be converted into AA, synthesis of prostaglandins (PGs) by a cyclooxygenase (COX) enzyme would be compromised, and this would seriously affect many normal metabolic processes. COX, also known as prostaglandin endoperoxide synthase (Pghs) or as prostaglandin G/H synthase, is a key membrane bound enzyme responsible for the oxidation of AA to PGs. Two COX isoforms have been identified, COX-1 and COX-2 that form PGH₂, a common precursor for the biosynthesis of thromboxane A₂ (TxA₂), prostacyclin (PGI₂) and PGs (PGD₂, PGE₂, PGF₂alpha). COX-1 enzyme is expressed constitutively in most cells and tissues. Its expression remains constant under either physiological or pathological conditions controlling synthesis of those PGs primarily involved in the regulation of homeostatic functions. In contrast, COX-2 is an intermediate response gene that encodes a 71-kDa protein. COX-2 is normally absent from most cells but highly inducible in certain cells in response to inflammatory stimuli resulting in enhanced PG release. PGs formed by COX-2 primarily mediate pain and inflammation but have multiple effects that can favour tumorigenesis. They are more abundant in cancers than in normal tissues from which the cancers arise. COX-2 is a participant in the pathway of colon carcinogenesis, especially when mutation of the APC (Adenomatous Polyposis Coli) tumour suppressor gene is the initiating event. In addition, COX-2 up-regulation and elevated PGE₂ levels are involved in breast carcinogenesis. It seems that there is a correlation between COX-2 level of expression and the size of the tumours and their propensity to

invade underlying tissue. Inhibition by non-steroidal anti-inflammatory drugs (NSAIDs) of COX enzymes which significantly suppress PGE₂ levels, reduced breast cancer incidence and protected against colorectal cancer. Therefore it is suggested that consumption of a diet enriched in n-3 PUFA (specifically EPA and DHA) and inhibition of COX-2 by NSAIDs may confer cardioprotective effects and provide a significant mechanism for the prevention and treatment of human cancers.

Protective effect of Hypericum perforatum Linn (St. John's wort) against hydrogen peroxide-induced apoptosis on human neuroblastoma cells.

Jang M, Lee T, Shin M, et al. *Neurosci Lett* 2002;329:177.

The medicinal plant *Hypericum perforatum* Linn, commonly known as St. John's wort, has been used as an antidepressant. To investigate whether St. John's wort possesses a protective effect against hydrogen peroxide (H₂O₂)-induced cytotoxicity in neuronal cells, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, 4,6-diamidino-2-phenylindole staining, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling assay, flow cytometry analysis, DNA fragmentation assay, and caspase-3 enzyme assay were performed on SK-N-MC human neuroblastoma cells. Cells treated with H₂O₂ exhibited several apoptotic features, while those pre-treated with St. John's wort prior to H₂O₂ exposure showed a decreased occurrence of apoptotic features. In addition, pre-treatment with St. John's wort inhibited H₂O₂-induced increase in caspase-3 enzyme activity. These results suggest that St. John's wort may exert a protective effect against H₂O₂-induced apoptosis in human neuroblastoma cells.

Cholesterol assimilation by lactic acid bacteria and Bifidobacteria isolated from the human gut.

Pereira DI, Gibson GR. *Appl Environ Microbiol* 2002;68:4689-4693.

The objective of this study was to evaluate the effect of human gut-derived lactic acid bacteria and bifidobacteria on cholesterol levels in vitro. Continuous cultures inoculated with fecal material from healthy human volunteers with media supplemented with cholesterol and bile acids were used to enrich for potential cholesterol assimilators among the indigenous bacterial populations. Seven potential probiotics were found: *Lactobacillus fermentum* strains F53 and KC5b, *Bifidobacterium infantis* ATCC 15697, *Streptococcus bovis* ATCC 43143, *Enterococcus durans* DSM 20633, *Enterococcus gallinarum*, and *Enterococcus faecalis*. A comparative evaluation regarding the in vitro cholesterol reduction abilities of these strains along with commercial probiotics was undertaken. The degree of acid and bile tolerance of strains was also evaluated. The human isolate *L. fermentum* KC5b was able to maintain viability for 2 h at pH 2 and to grow in a medium with 4,000 mg of bile acids per liter. This strain was also able to remove a maximum of 14.8 mg of cholesterol per g (dry weight) of cells from the culture medium and therefore was regarded as a candidate probiotic.

A new prebiotic from germinated barley for nutraceutical treatment of ulcerative colitis.

Bamba T, Kanauchi O, Andoh A, Fujiyama Y. *J Gastroenterol Hepatol* 2002;7:818-824.

A germinated barley foodstuff (GBF) containing glutamine-rich protein and hemicellulose-rich fiber was made from brewer's spent grain, by physical isolation. Our previous studies demonstrated that GBF supported maintenance of epithelial cell populations, facilitated epithelial repair, and suppressed epithelial nuclear factor kappaB-DNA-binding activity through generating increased short-chain fatty acid (especially butyrate) production by luminal microflora, which includes *Bifidobacterium* and *Eubacterium*, thereby preventing experimental colonic injury. The fiber fraction also modulates stool water content because of its high water-holding capacity. The patients with mild to moderate active ulcerative colitis who had been unresponsive to or intolerant of standard treatment received 20-30 g GBF, feeding daily in a non-randomized, open-label fashion. At 4 weeks, this treatment resulted in a significant clinical and endoscopic improvement. The improvement was associated with an increase in stool butyrate concentrations. These results indicate that GBF feeding is a potentially new, attractive prebiotic treatment in patients with ulcerative colitis. The potency of GBF on modulating microflora, as well as the high water-holding capacity, may play an important role in treatment and prolongation of remission in ulcerative colitis.

Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women.

Jenkins DJ, Kendall CW, Jackson CJ, et al. *Am J Clin Nutr* 2002;76:365-372.

BACKGROUND: Many of the benefits of soy have been attributed to soy isoflavones. **OBJECTIVE:** The objective was to determine the effects of high- and low-isoflavone soy-protein foods on both lipid and nonlipid risk factors for coronary artery disease (CAD). **METHODS:** Forty-one hyperlipidemic men and postmenopausal women participated in a study with three 1-mo diets: a low-fat dairy food control diet and high- (50 g soy protein and 73 mg isoflavones daily) and low- (52 g soy protein and 10 mg isoflavones daily) isoflavone soyfood diets. All 3 diets were very low in saturated fat (< 5% of energy) and cholesterol (< 50 mg/d). Fasting blood samples were drawn and blood pressure was measured at the start and end of each diet. **RESULTS:** No significant differences were seen between the high- and low-isoflavone soy diets. Compared with the control diet, however, both soy diets resulted in significantly lower total cholesterol, estimated CAD risk, and ratios of total to HDL cholesterol, LDL to HDL cholesterol, and apolipoprotein B to A-I. No significant sex differences were observed, except for systolic blood pressure, which in men was significantly lower after the soy diets than after the control diet. On the basis of blood lipid and blood pressure changes, the calculated CAD risk was significantly lower with the soy diets, by 10.1 +/- 2.7%. **CONCLUSION:** Substitution of soyfoods for animal products, regardless of isoflavone concentration, reduces the CAD risk because of both modest reductions in blood lipids and reductions in oxidized LDL, homocysteine, and blood pressure.

Interactions between the microbiota and the intestinal mucosa.

Schiffirin EJ, Blum S. *Eur J Clin Nutr* 2002;56:S60-S64.

The intestinal microflora can be considered as a postnatally acquired organ composed of a large diversity of bacterial cells that can perform different functions for the host. This organ is highly exposed to environmental influences and thus modulated in its composition and functions by external factors, such as nutrition. Specific components of the intestinal microflora, including lactobacilli and bifidobacteria, have been associated with beneficial effects on the host, such as promotion of gut maturation and integrity, antagonisms against pathogens and immune modulation. In addition, the microflora seem to play a significant role in the maintenance of intestinal immune homeostasis and prevention of inflammation. At the present time, the contribution of intestinal epithelial cell in the first line of defence against pathogenic bacteria and microbial antigens has been recognized, in contrast, the interactions of intestinal epithelial cells with commensal bacteria are less understood. The present work summarizes the increasing scientific attention for mechanisms of the innate immune response of the host to different components of the autochthonous microflora and suggests a potential role for selected probiotic bacteria in the regulation of intestinal inflammation.

Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells.

Sartippour MR, Shao ZM, Heber D, et al. *J Nutr* 2002;132:2307-2311.

Investigators have shown that green tea and its main catechin epigallocatechin-3 gallate (EGCG) may decrease the risk of cancer. Our previous study showed that green tea extract (GTE) as well as its individual catechin components inhibited MDA-MB231 breast cancer cell and human umbilical vein endothelial cell (HUVEC) proliferation. Further, GTE suppressed breast cancer xenograft size and decreased the tumor vessel density in vivo. In the current study, we investigated the effect of GTE on the major angiogenic factor vascular endothelial growth factor (VEGF) in an in vitro experiment. GTE or EGCG (40 mg/L) significantly decreased the levels of the VEGF peptide secreted into conditioned media. This occurred in both HUVEC and human breast cancer cells and the effect was dose dependent. Furthermore, GTE and EGCG decreased the RNA levels of VEGF in MDA-MB231 cells. This inhibition occurred at the transcriptional regulation level and was accompanied by a significant decrease in VEGF promoter activity. We also showed that GTE decreased c-fos and c-jun RNA transcripts, suggesting that activator protein (AP)-1-responsive regions present in the human VEGF promoter may be involved in the inhibitory effect of GTE. Furthermore, GTE suppressed the expression of protein kinase C, another VEGF transcription modulator, in breast cancer cells. Inhibition of VEGF transcription appeared to be one of the molecular mechanism(s) involved in the antiangiogenic effects of green tea, which may contribute to its potential use for breast cancer treatment and/or prevention.

Efficacy of St. John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial.

Lecrubier Y, Clerc G, Didi R, Kieser M. *Am J Psychiatry* 2002;159:1361-1366.

OBJECTIVE: In a double-blind, randomized, placebo-controlled trial with 375 patients the authors investigated the antidepressant efficacy and safety of 300 mg t.i.d. of hydroalcoholic *Hypericum perforatum* extract WS 5570. **METHOD:** The study participants were male and female adult outpatients with mild to moderate major depression (single or recurrent episode, DSM-IV criteria). After a single-blind placebo run-in phase, the patients were randomly assigned, 186 to WS 5570 and 189 to placebo, after which they received double-blind treatment for 6 weeks. Follow-up visits were held after 1, 2, 4, and 6 weeks. The primary outcome measure was the change from baseline in the total score on the 17-item Hamilton Depression Rating Scale. In addition, analyses of responders (patients with at least a 50% reduction in Hamilton total score) and patients with remissions (patients with a total score of 6 or less on the Hamilton scale at treatment end) were carried out, and subscale/subgroup analyses were conducted. The design included an adaptive interim analysis performed after random assignment of 169 patients with options for group size adjustment or early termination. **RESULTS:** Compared to placebo, WS 5570 produced a significantly greater reduction in total score on the Hamilton depression scale and significantly more patients with treatment response or remission. It was more effective in patients with higher baseline Hamilton scores and led to global reduction of depression-related core symptoms, assessed with the melancholia subscale of the Hamilton scale. The placebo and WS 5570 groups had comparable adverse events. **CONCLUSIONS:** *H. perforatum* extract WS 5570 was found to be safe and more effective than placebo for the treatment of mild to moderate depression.

Lead induced oxidative damage and its response to combined administration of alpha-lipoic acid and succimers in rats.

Pande M, Flora SJ. *Toxicology* 2002;177:187-196.

Alpha-lipoic acid (LA) has been reported to be highly effective in improving the thiol capacity of the cells and in reducing lead induced oxidative stress. These results suggested its possible role as a therapeutic intervention of lead poisoning in combination with a chelator. We investigated the effects of LA, either alone or when administered in combination with succimer (meso 2,3-dimercaptosuccinic acid; DMSA or one of its analogue monoisoamyl DMSA), in influencing the lead induced alterations in haem synthesis pathway, hepatic, renal and brain oxidative stress and lead concentration from blood and soft tissues. The results suggest a significant lead induced inhibition of delta-aminolevulinic acid dehydratase (ALAD), reduction in glutathione (GSH) and an increased zinc protoporphyrin (ZPP) level in blood, indicating altered heme synthesis pathway. Both the thiol chelators were able to increase blood ALAD activity and GSH level towards normal. The most prominent effect on blood ALAD activity was however observed when monoisoamyl DMSA (MiADMSA) was co-administered with LA. Lead exposure produced significant depletion of hepatic GSH, while, oxidized glutathione (GSSG), thiobarbituric acid reactive substances (TBARS) and catalase activity increased significantly, suggesting hepatic oxidative stress. All the treatments were able to increase hepatic GSH and reduce GSSG levels, while, TBARS level reduced significantly in animals administered LA and MiADMSA, individually or in combination. Lead induced increase in renal GSSG, TBARS levels and catalase activity, were effectively reduced by LA, while, the two chelators when administered alone were effective only in reducing GSSG and catalase activity. The most prominent beneficial effects, however, were observed in animals treated concomitantly with LA and one of the chelators (DMSA or MiADMSA). Brain GSH and GSSG levels decreased moderately while superoxide dismutase (SOD) activity remained statistically unaltered on lead exposure. Brain catalase activity, on the other hand,

increased significantly. Administration of LA was effective in reducing these alterations in the brain, however, the best effects were achieved in animals co-administered LA and one of the thiol chelators. The results point to a significant beneficial role of LA in the recovery of altered biochemical variables both during monotherapy and when given in combination with succimer. It however, showed no chelating properties in decreasing lead burden from blood, liver and kidneys except for a significantly more pronounced decrease in brain lead concentration in animals administered LA plus thiol chelators, compared to the effects of chelating agents alone. This is an interesting and notable observation, which requires further exploration. The results thus provide evidence of an encouraging role of LA when given in combination with a thiol chelator in the therapeutic intervention of lead poisoning, particularly in reducing the oxidative stress and brain lead concentration.

Ipriflavone inhibits osteolytic bone metastasis of human breast cancer cells in a nude mouse model.

Iwasaki T, Mukai M, Tsujimura T, et al. *Int J Cancer* 2002;100:381-387.

Osteolytic bone metastasis is a frequent problem in the treatment of cancer. Ipriflavone, a synthetic isoflavone that inhibits osteoclastic bone resorption, has been used for the treatment of osteoporosis in some countries. Some other isoflavones also exhibit an antitumor effect in vitro and in vivo. Here, we studied the effects of ipriflavone on osteolytic bone metastasis of MDA-231 human breast cancer cells injected intracardially into athymic nude mice (ICR-nu/nu). Daily oral administration of ipriflavone at 12 mg/mouse significantly inhibited the development of new osteolytic bone metastases ($p < 0.05$) and the progression of established osteolytic lesions ($p = 0.01$), prolonging the life of tumor-bearing mice ($p = 0.01$ vs. control). In addition, ipriflavone reduced the number of osteoclasts at the bone-cancer interface with no severe adverse effects on the host. In vitro, ipriflavone inhibited the proliferation and DNA synthesis of MDA-231 cells and blocked the ligand-induced phosphorylation of Tyr(845) of the EGFR. Ipriflavone did not promote apoptosis of MDA-231 cells. Our results show that ipriflavone not only directly inhibits the growth of cancer cells but also reduces osteoclasts to prevent the soft tissue tumor burden and osteolytic bone metastases. These findings raise the possibility that ipriflavone may be of use as a therapeutic agent against osteolytic bone metastasis.

Suppression of human pancreatic carcinoma cell growth and invasion by epigallocatechin-3-gallate.

Takada M, Nakamura Y, Koizumi T, et al. *Pancreas* 2002;25:45-48.

INTRODUCTION: The consumption of green tea is associated with a lower risk of several types of human carcinomas. A number of studies have focused on the possible mechanisms of cancer prevention by tea extracts, especially polyphenols such as epigallocatechin-3-gallate (EGCG). **AIMS AND METHODOLOGY:** Green tea-derived EGCG was tested in human pancreatic carcinoma cells. The cells (PANC-1, MIA PaCa-2, and BxPC-3) were treated with different doses of EGCG (0, 25, 50, 100, and 200 micromol/L) for 48 hours in culture medium. Proliferation of pancreatic carcinoma cells was measured by means of the WST-1 colorimetric assay. For the study of cell invasion, the cells were incubated with 100 micromol/L EGCG for 2 hours. Then, the cells were added into the cell insert, coated with Matrigel basement membrane matrix. After incubation at 37 degrees C for 24 hours, the cells that had invaded through the Matrigel were counted visually under the microscope. **RESULTS:** The growth of all three pancreatic carcinoma cells was significantly suppressed by EGCG treatment in a dose-dependent manner. EGCG treatment caused significant suppression of the invasive ability of pancreatic carcinoma cells PANC-1, MIA PaCa-2, and BxPC-3 but did not affect the cell cycle protein cyclin D1. **CONCLUSION:** EGCG may be a potent biologic inhibitor of human pancreatic carcinomas, reducing their proliferative and invasive activities.

S-Adenosyl-L-methionine and alcoholic liver disease in animal models. Implications for early intervention in human beings.

Lieber C. *Alcohol* 2002;27:173.

In patients with severe alcoholic liver disease (i.e., cirrhosis), a deficiency of S-adenosylmethionine (SAME) develops as a result of decreased SAME synthetase activity. Whether a sizeable SAME depletion occurs already at earlier stages of alcoholic liver disease has been the subject of debate. To address this issue, rats were fed alcohol (or isocaloric carbohydrate) in Lieber-DeCarli liquid diets containing adequate amounts of protein, vitamins, and lipotropic factors, including methionine. Alcohol feeding resulted in hepatic steatosis (without fibrosis) and unchanged SAME synthetase activity, yet SAME concentration was already greatly decreased. This most likely resulted from oxidative stress associated with the metabolism of alcohol and the induction of cytochrome P4502E1 (CYP2E1), which generates free radicals. Indeed, the decrease in hepatic SAME correlated with parameters of oxidative stress, such as increased 4-hydroxynonenal (measured by gas chromatography-mass spectrometry) and diminished glutathione (GSH). Decreased GSH, occurring as a result of excessive GSH consumption caused by the oxidative stress, probably generated by enhanced utilization of SAME, a precursor of GSH, thereby explaining the depletion of SAME. In view of the known differences between rodents and primates in the metabolism of lipotropes, my colleagues and I have also studied the interaction between alcohol and SAME in baboons and found again that, at early stages preceding the development of cirrhosis, there was already a significant lowering of hepatic SAME concentration, associated with a striking oxidative stress documented by decreased levels and accelerated turnover of GSH. This was associated with increased lipid peroxidation and damage to cellular membranes, including those of the mitochondria, assessed by electron microscopy. Oral administration of SAME resulted in its hepatic repletion with a corresponding attenuation of the ethanol-induced oxidative stress and liver injury, with significantly less GSH depletion, less increases in plasma aspartate aminotransferase (AST) levels, less leakage of mitochondrial glutamic dehydrogenase into the plasma, and fewer megamitochondria.

In conclusion, (1) both in rodents and in non-human primates, significant SAME depletion occurs already at early stages of alcoholic liver disease, despite the consumption of adequate diets; (2) the decreased hepatic SAME concentration and the associated liver lesions, including mitochondrial injury, can be corrected with SAME supplementation; and (3) accordingly, therapeutic administration of SAME should be the subject of a comprehensive clinical trial to assess its capacity to attenuate early stages of alcoholic liver injury in human beings.

Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension.

Rivas M, Garay RP, Escanero JF, et al. *J Nutr* 2002;132:1900-1902.

Soy-based diets reduce blood pressure in spontaneously hypertensive rats, but apparently not in hypertensive humans. In the present study, the antihypertensive potential of soy milk (500 mL twice daily) compared with cow's milk was investigated in a 3-mo double-blind randomized study of 40 men and women with mild-to-moderate hypertension. Before initiation of the study, urinary isoflavonoids (measured by HPLC) were undetectable in most cases (for genistein, they were always <100 micromol/L). After 3 mo of soy milk consumption, systolic blood pressure decreased by 18.4 +/- 10.7 mmHg compared with 1.4 +/- 7.2 mmHg in the cow's milk group (P < 0.0001), diastolic blood pressure decreased by 15.9 +/- 9.8 mmHg vs. 3.7 +/- 5.0 mmHg in the cow's milk group (P < 0.0001) and mean blood pressure decreased by 16.7 +/- 9.0 mmHg compared with 3.0 +/- 4.6 mmHg in the cow's milk group (P < 0.0001). Urinary genistein was strongly (r = -0.588) and significantly (P = 0.002) correlated with the decrease in blood pressure, particularly for diastolic values. In conclusion, chronic soy milk consumption had modest, but significant hypotensive action in essential hypertensive subjects. This hypotensive action was correlated with the urinary excretion of the isoflavonoid genistein.

Isoflavones inhibit proliferation of ovarian cancer cells in vitro via an estrogen receptor-dependent pathway.

Chen X, Anderson JJ. *Nutr Cancer* 2001;41:165-171.

Incidence rates of ovarian cancer remain lowest in Asian nations, which consume diets rich in soy products, whereas they remain among the highest in the United States and other Western nations, which consume low amounts of soy foods. The hypothesis of this study is that soy-derived isoflavones inhibit the proliferation of ovarian cancer cells in vitro by regulating cytokine synthesis. Cell proliferation was evaluated by bromodeoxyuridine and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. DNA synthesis of Caov-3 and NIH:OVCAR-3, two ovarian cancer cell lines, was significantly inhibited by genistein or daidzein at dietarily relevant concentrations (10(-8)-10(-10) M). Also, the number of viable cells was significantly lower (45-75%) in all isoflavone-treated groups than in the control group ($P < 0.01$). The addition of ICI-182780, an estrogen antagonist, blocked these inhibitory effects. In addition, interleukin-6 synthesis by these two cell lines was inhibited by genistein or daidzein; production was decreased by approximately 20% compared with the control group ($P < 0.05$). In contrast, transforming growth factor-beta 1 production in ovarian cancer cells incubated with genistein or daidzein was significantly greater, i.e., by approximately 30%, than in the control group ($P < 0.05$). Addition of ICI-182780 also neutralized the effects of isoflavones on the production of these two cytokines by ovarian cancer cells. In summary, genistein and daidzein independently modify cytokine production and reduce ovarian cancer cell proliferation via, at least in part, an estrogen receptor-dependent pathway.

Kava – the Unfolding Story: Report on a Work-in-Progress.

Denham A, McIntyre M, Whitehouse J. *J Altern Complement Med* 2002;8:237-263.

This paper, originated as a submission (now updated) to the U.K. Medicines Control Agency and Committee of Safety of Medicines (CSM) on January 11, 2002, in response to a report circulated by the German Federal Institute for Drugs and Medical Products (German initials are BfArM), a compilation of which is summarized in Appendix 2. This agency issued notification in late November 2001 of some thirty adverse events associated with the use of concentrated standardized preparations of kava (*Piper methysticum*, Forst. f.) reported from Germany and Switzerland. An analysis of the summary of the BfArM case reports (see Appendix 2) shows that these contain duplications among the cases cited. The original submission that was sent to the CSM January 2002 has been updated to the version published here. This new version was completed in April 2002. As a result of the alert from BfArM, the evaluation of kava's safety is now occurring on a worldwide basis and, being that this a matter of considerable importance to the public, the health care community, and regulatory authorities as well as to kava farmers throughout Polynesia, it is important to depict this progress report. As such, this updated report does not provide final answers. The material released by the BfArM is lacking in detail; however, it is hoped that this report will shed light on the kava controversy. It is anticipated that there will be further updates shortly. This report, prepared on behalf of the Traditional Medicines Evaluation Committee, a subcommittee of the European Herbal Practitioners Association, argues that many of the adverse events cited by the BfArM should not be attributed to kava. In addition, the report states that the properties of concentrated standardized kava extracts - as opposed to preparations that closely approximate those created for traditional use - contribute to causing adverse events. This report proposes a number of simple measures that will ensure that safe kava preparations may continue to be available in the United Kingdom.

**Burning mouth syndrome (BMS):
double blind controlled study of
alpha-lipoic acid (thioctic acid)
therapy.**

Femiano F, Scully C. *J Oral Pathol Med* 2002;31:267-269.

BACKGROUND: Burning mouth syndrome (BMS) has features of a neuropathy and could be related to the production of the toxic free radicals that are released in stress situations. Alpha-lipoic acid is an antioxidant able to increase the levels of intracellular glutathione and eliminate free radicals. This study aimed to examine the effectiveness of alpha-lipoic acid in the therapy of BMS. **METHOD:** This was a double blind, controlled study conducted for two months on 60 patients with constant BMS. Comparing alpha-lipoic acid (test) with cellulose starch (placebo), there was no laboratory evidence of deficiencies in iron, vitamins or thyroid function and no hyperglycaemia. **RESULTS AND CONCLUSION:** Following treatment with alpha-lipoic acid, there was a significant symptomatic improvement, compared with placebo, with the majority showing at least some improvement after 2 months, thus supporting the hypothesis that burning mouth syndrome is a neuropathy. This improvement was maintained in over 70% of patients at the 1 year follow-up.

**Bioflavonoids: proanthocyanidins
and quercetin and their potential
roles in treating musculoskeletal
conditions.**

Teixeira S. *J Orthop Sports Phys Ther* 2002;32:357-363.

As a clinician treating musculoskeletal conditions, one is continually in search of safe and more effective treatment methods that will hasten tissue healing. Chronic inflammation has been shown to cause connective tissue degradation. Typically, nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids are used to control the inflammatory process, however, long-term use has been associated with potentially serious side effects. The purpose of this article is to introduce and describe literature on 2 natural compounds, namely, proanthocyanidin (PCO) and quercetin, which are 2 specific types of bioflavonoids, and to discuss their potential benefits in treating musculoskeletal conditions. There is evidence to suggest that flavonoids may be beneficial to connective tissue for several reasons, which include the limiting of inflammation and associated tissue degradation, the improvement of local circulation, as well as the promoting of a strong collagen matrix. An overview of bioflavonoids as well as relevant research, safety issues, absorption, and specific sources of PCO and quercetin in foods and through supplementation is included.

Effect of homocysteine-lowering therapy with folic acid, vitamin B(12), and vitamin B(6) on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial.

Schnyder G, Roffi M, Flammer Y, et al. *JAMA* 2002;288:973-979.

CONTEXT: Plasma homocysteine level has been recognized as an important cardiovascular risk factor that predicts adverse cardiac events in patients with established coronary atherosclerosis and influences restenosis rate after percutaneous coronary intervention. **OBJECTIVE:** To evaluate the effect of homocysteine-lowering therapy on clinical outcome after percutaneous coronary intervention. **DESIGN, SETTING, AND PARTICIPANTS:** Randomized, double-blind placebo-controlled trial involving 553 patients referred to the University Hospital in Bern, Switzerland, from May 1998 to April 1999 and enrolled after successful angioplasty of at least 1 significant coronary stenosis ($>$ or = 50%). **INTERVENTION:** Participants were randomly assigned to receive a combination of folic acid (1 mg/d), vitamin B(12) (cyanocobalamin, 400 micro g/d), and vitamin B(6) (pyridoxine hydrochloride, 10 mg/d) (n = 272) or placebo (n = 281) for 6 months. **MAIN OUTCOME MEASURE:** Composite end point of major adverse events defined as death, nonfatal myocardial infarction, and need for repeat revascularization, evaluated at 6 months and 1 year. **RESULTS:** After a mean (SD) follow-up of 11 (3) months, the composite end point was significantly lower at 1 year in patients treated with homocysteine-lowering therapy (15.4% vs 22.8%; relative risk [RR], 0.68; 95% confidence interval [CI], 0.48-0.96; P = .03), primarily due to a reduced rate of target lesion revascularization (9.9% vs 16.0%; RR, 0.62; 95% CI, 0.40-0.97; P = .03). A nonsignificant trend was seen toward fewer deaths (1.5% vs 2.8%; RR, 0.54; 95% CI, 0.16-1.70; P = .27) and nonfatal myocardial infarctions (2.6% vs 4.3%; RR, 0.60; 95% CI, 0.24-1.51; P = .27) with homocysteine-lowering therapy. These findings remained unchanged after adjustment for potential confounders. **CONCLUSION:** Homocysteine-lowering therapy with folic acid, vitamin B(12), and vitamin B(6) significantly decreases the incidence of major adverse events after percutaneous coronary intervention.

Decreased levels of coenzyme Q10 in patients with bronchial asthma.

Gazdik F, Gvozdjakova A, Nadvornikova R, et al. *Allergy* 2002;57:811-814.

BACKGROUND: The contribution of free oxygen radicals in the pathogenesis of bronchial asthma is generally accepted. The modulation of antioxidative defence by supplementation with antioxidants represents additive therapy in complex management of disease. The aim of the study was to assess the levels of coenzyme Q10, alpha-tocopherol, and beta-carotene both in plasma and whole blood, and malondialdehyde (MDA) and eosinophil cationic protein (ECP) in plasma of asthmatics (As). **METHODS:** Fifty-six As (15 males and 41 females) aged from 19 to 72 years (mean age 46 years) suffering from allergic asthma were enrolled into the study. The control group comprised 25 healthy volunteers (16 males, 9 females) aged 25-50 years. **RESULTS:** The concentrations of CoQ10 decreased significantly both in plasma and whole blood, compared with healthy volunteers (0.34 +/- 0.15 microM/l vs. 0.52 +/- 0.15 microM/l, 0.33 +/- 0.14 microM/l vs. 0.50 +/- 0.13 microM/l, P < 0.001, P < 0.001, respectively). The levels of alpha-tocopherol were decreased both in plasma and whole blood in comparison with controls [24.10 microM/l (19.8; 30.5), vs. 33.20 microM/l (28.25; 38.05), 17.22 +/- 6.45 microM/l vs. 21.58 +/- 7.92 microM/l, P = 0.006, P = 0.01, respectively]. The levels of MDA were elevated over the reference range in both groups (reference range < 4.5 microM/l). No changes were seen in beta-carotene concentrations. Positive correlation was found between whole blood CoQ10 and alpha-tocopherol concentrations. **CONCLUSION:** Results of the study suggest a possible contribution of suboptimal concentrations of CoQ10 on antioxidative dysbalance in As and provide a rationale for its supplementation.

Abnormal methyl metabolism in pancreatic toxicity and diabetes.

Longnecker DS. *J Nutr* 2002;132:2373S-2376S.

Several experimental studies suggest that disturbed methylation can influence cellular differentiation in the pancreas and contribute to toxic injury in ways that enhance the pathogenesis of pancreatitis and carcinogenesis. In vitro development of fetal rat pancreas requires a basal level of methionine, but full differentiation requires a higher methionine level. Involvement of methylation in normal differentiation is supported by reports of development of hepatocyte-like cells in the pancreas of rats fed a choline-deficient diet. The administration of ethionine by feeding to mice in a choline-sufficient diet caused a lower incidence of acute hemorrhagic pancreatitis than in mice given a choline-deficient diet. Feeding or injections of ethionine in choline-sufficient diets induces low grade pancreatitis and pancreatic atrophy in rats. In the N-nitrosobis(2-oxopropyl)amine-induced model of ductal adenocarcinoma in hamsters, the latent period for induction of carcinomas has been dramatically reduced by the intermittent feeding of a choline-deficient diet combined with ethionine treatment. A recent epidemiologic study in smokers indicates that the risk of pancreatic carcinoma is inverse to serum levels of folate. These studies suggest that compromised methyl metabolism might be associated with pancreatic cancer risk in humans. Finally, it has recently been demonstrated that serum homocysteine and erythrocyte S-adenosylhomocysteine levels are elevated, and erythrocyte S-adenosylmethionine content is reduced in patients with diabetes mellitus and renal failure, likely reflecting disturbed methylation pathways. The latter may contribute to the pathogenesis of complicating lesions in diabetes. These studies suggest that disturbed methyl metabolism may contribute to the pathogenesis of several pancreatic diseases.

Vitamin A status in children with asthma.

Arora P, Kumar V, Batra S. *Pediatr Allergy Immunol* 2002;13:223-226.

Low vitamin A levels have been found in a number of diseases in children. The aim of this study was to examine the vitamin A status in children with asthma and to correlate the changes with severity of disease. Serum levels of vitamin A, retinol-binding protein (RBP), and albumin were estimated in 35 asthmatic children (24 males) in the age group of 2-12 years (mean 5.89 years) and 29 controls (19 males). Both study and control groups were similar with respect to age, sex, and overall nutritional status. Twenty-four children in the study group (68.6%) had moderate to severe persistent asthma and eight children had mild persistent asthma. Only three patients suffered from mild intermittent asthma. Vitamin A levels in children with asthma (mean +/- SD 22.14 +/- 5.38 microg/dl) were found to be significantly lower than their controls (mean +/- SD 27.54 +/- 4.83 microg/dl) ($p = 0.0001$). Age, age of onset of asthma, and gender had no correlation with serum vitamin A levels. Low serum vitamin A levels (< 20 microg/dl) were observed four times more commonly in the study group (28.6%) than controls (6.9%). Severity of asthma had a negative correlation with serum vitamin A levels ($r = -0.61$, $p = 0.0001$). Children with severe persistent asthma had markedly low serum vitamin A levels (mean +/- SD 13.42 +/- 5.19 microg/dl) as compared with mild intermittent asthma (mean +/- SD 24.61 +/- 2.32 microg/dl). Therapeutic trials are needed to prove whether low vitamin A levels contribute to asthma severity and the clinical utility of vitamin A supplementation in asthmatic children.

Effect of folate supplementation on mucosal cell proliferation in high risk patients for colon cancer.

Khosraviani K, Weir HP, Hamilton P, et al. *Gut* 2002;51:195-199.

AIMS: Intracellular folate deficiency has been implicated in colonic carcinogenesis in epidemiological studies and animal and human cancer models. Our aim was to determine the effect of folate supplementation on patients with recurrent adenomatous polyps using rectal mucosal cell proliferation as a biomarker. **PATIENTS AND METHODS:** Eleven patients with recurrent adenomatous polyps of the colon were randomised into a treatment group (n=6) receiving a dietary supplement of 2 mg folic acid per day for three months and a control group (n=5) receiving a placebo. Rectal biopsies were taken at 10 cm from the anal verge prior to supplementation and repeated at four, 12, and 18 weeks from the start of the supplementation. Each biopsy was immediately incubated in culture medium enriched with bromodeoxyuridine (BrdU). The S phase cells which incorporated BrdU into their DNA were identified following immunohistochemical staining. Twenty five orientated crypts were identified for each time point and the number and position of BrdU positive and BrdU negative cells were counted. BrdU labelling indices (LIs) were calculated for the entire crypt and for each of five equal compartments running consequently from the base to the luminal surface. **RESULTS:** The LI of the treatment group (9.1 (6.7, 12.3)) and the control group (9.3 (7.8, 10.3)) were comparable at the start. Over the duration of the supplementation period, LI in the control group did not alter significantly (9.3 (7.8, 10.3) v 9.6 (8.9, 10.4)). However, LI of the folate treated group was lowered after 12 weeks of supplementation (9.1 (6.7, 12.3) v 7.4 (5.3, 9.6)). Analysis of the LI for compartments within the crypt showed that the most significant drop in number of proliferating cells was in the upper most regions of the crypt. **CONCLUSION:** These data indicate that (a) folate supplementation decreases colonic mucosal cell proliferation in a high risk group for colon cancer and (b) the most significant reduction takes place at the luminal aspect of the crypt.

Regulation and perturbation of testicular functions by vitamin A.

Livera G, Rouiller-Fabre V, Pairault C, et al. *Reproduction* 2002;124:173-180.

In addition to playing a fundamental role in very diverse processes such as vision and the growth and differentiation of numerous types of cell, vitamin A (retinol) and its principal biologically active derivative, retinoic acid, are clearly involved in the regulation of testicular functions in rodents. An excess of vitamin A leads to testicular lesions and spermatogenic disorders, and a deficiency induces early cessation of spermatogenesis and adversely affects testosterone secretion. Furthermore, mice mutant for retinoic acid alpha receptors and retinoid X beta receptors are sterile. Retinoids appear to exert an action on the three main testicular types of cell (Sertoli, germinal and Leydig cells), as they act on the signalling pathways and Sertoli cell metabolism, and modify numerous factors secreted in Sertoli cells. Retinoids also appear to be necessary for the proliferation and differentiation of A spermatogonia, and for spermiogenesis. In addition, vitamin A deficiency leads to atrophy of the accessory sex organs after decreased testosterone production. Recent studies have shown that retinoids already affect these three types of cell in fetuses. Curiously, the effects of retinoids on fetal and adult testis seem opposed.

Vitamin E and cognitive decline in older persons.

Morris MC, Evans DA, Bienias JL, et al. *Arch Neurol* 2002;59:1125-1132.

BACKGROUND: Previous studies raise the possibility that antioxidants protect against neurodegenerative diseases. **OBJECTIVE:** To examine whether intake of antioxidant nutrients, including vitamin E, vitamin C, and carotene, is associated with reduced cognitive decline with age. **DESIGN:** Longitudinal population-based study conducted from September 17, 1993, to November 20, 2000, with an average follow-up of 3.2 years. **PATIENTS:** The patients were 2889 community residents, aged 65 to 102 years, who completed a food frequency questionnaire, on average 18 months after baseline. **MAIN OUTCOME MEASURE:** Cognitive change as measured by 4 tests (the East Boston Memory Test, which tests immediate and delayed recall; the Mini-Mental State Examination; and the Symbol Digit Modalities Test) at baseline and 3 years for all participants, and at 6 months for 288 randomly selected participants. **RESULTS:** We used random-effects models to estimate nutrient effects on individual change in the average score of the 4 cognitive tests. The cognitive score declined on average by 5.0×10^{-2} standardized units per year. There was a 36% reduction in the rate of decline among persons in the highest quintile of total vitamin E intake (-4.3×10^{-2} standardized units per year) compared with those in the lowest quintile (-6.7×10^{-2} standardized units per year) ($P = .05$), in a model adjusted for age, race, sex, educational level, current smoking, alcohol consumption, total calorie (energy) intake, and total intakes of vitamin C, carotene, and vitamin A. We also observed a reduced decline with higher vitamin E intake from foods ($P = .03$ for trend). There was little evidence of association with vitamin C or carotene intake. **CONCLUSION:** Vitamin E intake, from foods or supplements, is associated with less cognitive decline with age.

D-alpha-tocopheryl succinate (vitamin E) enhances radiation-induced chromosomal damage levels in human cancer cells, but reduces it in normal cells.

Kumar B, Jha MN, Cole WC, et al. *J Am Coll Nutr* 2002;21:339-343.

OBJECTIVE: The purpose of this study was to measure and compare the effect of d-alpha-tocopheryl succinate (alpha-TS) in modifying radiation-induced chromosomal damage in human normal cells and cancer cells in culture. **METHODS:** Three human normal fibroblast cell lines (GM2149, AG1522 and HF19) and three human cancer cell lines, cervical cancer (HeLa) and ovarian carcinoma cells (OVGI and SKOV3) were treated with alpha-TS (37.6 microM) 20 hours before 100 cGy gamma-irradiation. After 30 minutes of irradiation, colcemid was added and cells were fixed. One hundred randomly selected metaphase cells were scored for the presence of chromatid gaps and breaks. To study the cellular accumulation of alpha-TS, cells were incubated in the presence of alpha-TS (18.8 and 37.6 microM) for 24 hours, and alpha-TS was extracted with hexane using a-tocopheryl acetate as an internal standard. The levels of alpha-TS were determined by HPLC. **RESULTS:** Results showed that alpha-TS induced chromosomal damage in both human cervical cancer cells and ovarian cancer cells, but not in human normal fibroblasts in culture. In addition, alpha-TS enhanced the level of radiation-induced chromosomal damage in cancer cells, but it protected normal cells against such damage. Both cancer cells and normal cells accumulated similar levels of alpha-TS, suggesting that increased sensitivity of cancer cells to alpha-TS is acquired during transformation. **CONCLUSION:** The use of alpha-TS during radiation therapy may improve the efficacy of radiation therapy by enhancing tumor response and decreasing some of the toxicities on normal cells.

Interactions of copper with glycated proteins: possible involvement in the etiology of diabetic neuropathy.

Eaton JW, Qian M. *Mol Cell Biochem* 2002;234-235:135-142.

Humans and animals with diabetes frequently develop peripheral vascular dysfunction and peripheral neuropathies. There is accumulating evidence that impaired peripheral nerve function may derive from diminished endoneurial blood flow. The decrements in nerve blood flow may, in turn, be due to diminished endothelium-dependent vasodilation. Although a number of possible causes of this defective vasodilation have been suggested, none has been definitely proven. Regardless of the precise cause, the impaired vasodilatory activity may reflect diminished availability of endothelium-derived relaxing factor (EDRF), variously thought to be nitric oxide or thiol adducts of nitric oxide. Other investigators have reported that administration of transition metal chelators to diabetic rats corrects EDRF-mediated arterial relaxation and restores both neural blood flow and nerve conduction velocity, suggesting the involvement of transition metals. Our investigations center about the hypothesis that glycated proteins bind transition metals such as copper and iron, and that such 'glycochelates' accumulate within the vasculature in diabetes and catalytically inactivate EDRF. In partial support of this hypothesis: (1) Glycated albumin binds approximately 3-fold greater amounts of both copper and iron. (2) Copper bound to glycated albumin remains redox active (e.g. capable of supporting the oxidation of ascorbic acid). (3) Copper and copper-containing glycochelates cause the rapid decomposition of one putative form of EDRF, nitrosocysteine. (4) The amount of exchangeable (i.e. chelatable) copper in the plasma of diabetic rats is approximately twice that in normal rat plasma. (5) Similarly, tail tendons of diabetic animals have about twice as much bound copper as do tendons of normal rats. (6) Implants bearing adsorbed glycated albumin placed in the peritonea of normal mice for 48 h accumulate approximately 5 times as much bound copper as do implants coated with control albumin. Overall, these observations support—but do not conclusively prove—the hypothesis that transition metals such as copper, bound to glycated proteins, may blunt normal EDRF-dependent relaxation of diabetic arteries and provide a rationale for the use of transition metal chelators in the therapy of diabetic vasculopathy and neuropathy.

Vitamin C therapy ameliorates vascular endothelial dysfunction in treated patients with homocystinuria.

Pullin CH, Bonham JR, McDowell IF, et al. *J Inherit Metab Dis* 2002;25:107-118.

OBJECTIVES: We sought to investigate the effects of short- and long-term vitamin C therapy on endothelial dysfunction in patients with homocystinuria. **BACKGROUND:** Untreated homocystinuria due to cystathionine beta-synthase deficiency is associated with premature atherothrombotic disease; 25% of untreated patients suffer a vascular event by the age of 16 years and 50% by 29 years. Treatment directed at reducing homocysteine accumulation significantly reduces this risk. However, despite 'optimal' treatment and compliance, hyperhomocysteinaemia usually persists and individuals exhibit endothelial dysfunction indicative of an adverse cardiovascular prognosis. Additional intervention is therefore required to further reduce cardiovascular risk. **METHODS:** We investigated the endothelial effects of acute (2 g single dose) and chronic (1 g/day for 6 months) administration of oral vitamin C in 5 patients with homocystinuria (mean age 26 years, 1 male) and 5 age- and sex-matched controls. Brachial artery endothelium-dependent flow-mediated dilatation (FMD) and endothelium-independent responses to nitroglycerin (NTG) were measured using high-resolution ultrasonic vessel wall-tracking. **RESULTS:** Baseline: Plasma total homocysteine was 100.8 +/- 61.6 and 9.2 +/- 1.9 micromol/L in the patient and control groups, respectively ($p < 0.001$). FMD responses were impaired in the patient group (20 +/- 40 microm) compared with the controls (116 +/- 30 microm) ($p < 0.001$). Vitamin C administration: FMD responses in the patient group improved both acutely, 160 +/- 65 microm at 4 h ($p < 0.001$), and chronically, 170 +/- 70 microm at 2 weeks ($p < 0.001$) and 170 +/- 40 microm at 6 months ($p < 0.001$). FMD responses in the control group were unaltered ($p = 0.526$). Within both groups, neither the vascular response to NTG nor plasma homocysteine was altered ($p > 0.4$). **CONCLUSIONS:** Vitamin C ameliorates endothelial dysfunction in patients with homocystinuria, independent of changes in homocysteine concentration and should therefore be considered as an additional adjunct to therapy to reduce the potential long-term risk of atherothrombotic disease.

Effect of glutathione infusion on leg arterial circulation, cutaneous microcirculation, and pain-free walking distance in patients with peripheral obstructive arterial disease: a randomized, double-blind, placebo-controlled trial.

Arosio E, De Marchi S, Zannoni M, et al. *Mayo Clin Proc* 2002;77:754-759.

OBJECTIVE: To assess the effects of glutathione on pain-free walking distance (PFWD) and hemodynamic parameters in patients with peripheral artery disease. **PATIENTS AND METHODS:** Forty patients with Fontaine stage II peripheral artery disease who were seen between September 2000 and March 2001 at the vascular laboratory and ward of the Division of Vascular Medicine and Rehabilitation at Verona University were studied in a double-blind, placebo-controlled trial. The patients were randomly assigned (20 per group) to treatment with intravenous glutathione twice a day or saline solution twice a day for 5 days. Treatments were administered in a double-blind manner. The 2 groups of patients underwent measurement of PFWD by strain-gauge plethysmography and laser Doppler flowmetry (with postischemic test) of the symptomatic leg at rest and after treadmill test. All measurements and tests were repeated 12 hours after the last infusion. **RESULTS:** Between the 2 groups, hemodynamic tests showed no differences in baseline values and at rest after treatment. At rest, no differences were observed between basal and posttreatment values; findings in the saline group were similar during tests before and after the infusion period. In the glutathione group, we observed increases in PFWD (196+/-15 vs 143+/-11 m; $P<.04$), macrocirculatory flow after treadmill test with plethysmography at the end of treatment (9.3+/-2 vs 2.8+/-0.5 mL per 100 mL/min; $P<.002$), and postischemic hyperemia with laser Doppler flowmetry, registered as perfusion units (PU), at the end of infusions (14.4+/-3.2 vs 6.18+/-1.5 PU; $P<.005$), with a greater area under the curve after treatment (705+/-103 vs 508+/-45 PU/s; $P<.001$) and reduced time to flow motion (32+/-4 vs 48+/-11 seconds; $P<.05$). **CONCLUSION:** In patients with peripheral artery disease, glutathione prolongs PFWD and shows an improvement of macrocirculatory and microcirculatory parameters.

Usefulness of the Helicobacter pylori stool antigen test for detection Helicobacter pylori infection.

Altindis M, Dilek ON. *Acta Gastroenterol Belg* 2002;65:74-76.

Several diagnostic tests are available for evaluating *Helicobacter pylori* (*H. pylori*) infection: histological examination, culture of gastric biopsy specimens, rapid urease test, urea breath test and serology. In this study, we assessed the reliability of a newly developed enzyme immunoassay HpSA (*H. pylori* Stool Antigen) kit for detecting *H. pylori* antigen in stool. Eighty-five patients (50 males, 35 females; mean age 41.6 +/- 9.8 years) with dyspeptic symptoms who were examined by upper gastrointestinal endoscopy. The patients with a history of previous treatment with proton pump inhibitors, bismuth compounds or antibiotics were excluded. During the endoscopic examination biopsies were taken from antrum and corpus for rapid urease test and histological examination. Stool specimens were submitted to the laboratory and HpSA test was performed. *H. pylori* was considered in condition with rapid urease test and histopathological examination for *H. pylori* positive. Forty-six of 85 patients were positive and remaining 39 patients were negative for *H. pylori* with the rapid urease test and pathologic evaluation. When 0.160 was adopted as the cut-off value, in accordance with the manufacturer's recommendations; stool antigen has been detected in 45 of the 46 *H. pylori* positive patients. The sensitivity and specificity of HpSA test were 97.8%, 94.9% respectively. These results indicate that HpSA is a highly reliable diagnostic method for *H. pylori* infection.

Vitamin supplement use in a low-risk population of US male physicians and subsequent cardiovascular mortality.

Muntwyler J, Hennekens CH, Manson JE, et al. *Arch Intern Med* 2002;162:1472-1476.

BACKGROUND: Although basic research suggests that vitamins may have an important role in the prevention of cardiovascular diseases (CVD), the data from cohort studies and clinical trials are inconclusive. **METHODS:** This prospective cohort study was conducted among 83,639 male physicians residing in the United States who had no history of CVD or cancer. At baseline, data on use of vitamin E, ascorbic acid (vitamin C), and multivitamin supplements were provided by a self-administered questionnaire. Mortality from CVD and coronary heart disease (CHD) was assessed by death certificate review. **RESULTS:** Use of supplements was reported by 29% of the participants. During a mean follow-up of 5.5 years, 1037 CVD deaths occurred, including 608 CHD deaths. After adjustment for several cardiovascular risk factors, supplement use was not significantly associated with total CVD or CHD mortality. For vitamin E use, the relative risks (RRs) were 0.92 (95% confidence interval [CI], 0.70-1.21) for total CVD mortality and 0.88 (95% CI, 0.61-1.27) for CHD mortality; for use of vitamin C, the RRs were 0.88 (95% CI, 0.70-1.12) for total CVD mortality and 0.86 (95% CI, 0.63-1.18) for CHD mortality; and for use of multivitamin supplements, the RRs were 1.07 (95% CI, 0.91-1.25) for total CVD mortality and 1.02 (95% CI, 0.83-1.25) for CHD mortality. **CONCLUSIONS:** In this large cohort of apparently healthy US male physicians, self-selected supplementation with vitamin E, vitamin C, or multivitamins was not associated with a significant decrease in total CVD or CHD mortality. Data from ongoing large randomized trials will be necessary to definitely establish small potential benefits of vitamin supplements on subsequent cardiovascular risk.

Antioxidant neuroprotection in Alzheimer's disease as preventive and therapeutic approach.

Behl C, Moosmann B. *Free Radic Biol Med* 2002;33:182-191.

Various neurodegenerative disorders and syndromes are associated with oxidative stress. The deleterious consequences of excessive oxidations and the pathophysiological role of reactive oxygen species (ROS) have been intensively studied in Alzheimer's disease (AD). Neuronal cell dysfunction and oxidative cell death caused by the AD-associated amyloid beta protein may causally contribute to the pathogenesis of AD. Antioxidants that prevent the detrimental consequences of ROS are consequently considered to be a promising approach to neuroprotection. While there is ample experimental evidence demonstrating neuroprotective activities of antioxidants in vitro, the clinical evidence that antioxidant compounds act as protective drugs is still relatively scarce. Nevertheless, antioxidants constitute a major part of the panel of clinical and experimental drugs that are currently considered for AD prevention and therapy. Here, focus is put mainly on phenolic antioxidant structures that belong to the class of direct antioxidants. Experimental and clinical evidence for the neuroprotective potential of alpha-tocopherol (vitamin E) and 17beta-estradiol (estrogen) is shortly summarized and an outlook is given on possible novel antioxidant lead structures with improved pharmacological features.

An evaluation of antiretroviral therapy associated with alpha-tocopherol supplementation in HIV-infected patients.

Spada C, Treitinger A, Reis M, et al.
Clin Chem Lab Med 2002;40:456-459.

In HIV-infected patients, an increase in the production of oxygen-reactive species (ROS) is observed, with a consequent reduction of plasma levels of antioxidants such as alpha-tocopherol. The nuclear transcription factor-kappaB (NF-kappaB) is activated by a prooxidant state in the infected T cells through the release of its inhibitory subunit I-kappaB. The aim of the present work was to evaluate the behavior of hematological parameters and markers of anemia in HIV-infected patients who underwent antiretroviral therapy associated with 800 mg/day alpha-tocopherol supplementation. Blood samples were collected from supplemented (n=9) and not-supplemented (n=9) HIV-seropositive patients (n=18). We observed a decreased viral load in the alpha-tocopherol-supplemented group ($p < 0.05$); other changes, such as an increase in the CD4/CD8 ratio, in the hematocrit and in the hemoglobin concentration were also observed, though lacking statistical significance. We conclude that antiretroviral therapy in association with alpha-tocopherol (800 mg/day) supplementation is more effective in reducing viral load levels and also, possibly, in recovering other hematological parameters after a 60-day period of use.

Maternal loading with very low-density lipoproteins stimulates fetal surfactant synthesis.

Ryan AJ, Medh JD, McCoy DM, et al.
Am J Physiol Lung Cell Mol Physiol 2002;283:310-318.

We examined whether administration of very low-density lipoproteins (VLDL) to pregnant rats increases surfactant phosphatidylcholine (PtdCho) content in fetal pre-type II alveolar epithelial cells. VLDL-triglycerides are hydrolyzed to fatty acids by lipoprotein lipase (LPL), an enzyme activated by heparin. Fatty acids released by LPL can incorporate into the PtdCho molecule or activate the key biosynthetic enzyme cytidyltransferase (CCT). Dams were given BSA, heparin, VLDL, or VLDL with heparin intravenously. Radiolabeled VLDL given to the pregnant rat crossed the placenta and was distributed systemically in the fetus and incorporated into disaturated PtdCho (DSPtdCho) in pre-type II cells. Maternal administration of VLDL with heparin increased DSPtdCho content in cells by 45% compared with control ($P < 0.05$). VLDL produced a dose-dependent, saturable, and selective increase in CCT activity. VLDL did not significantly alter immunoreactive CCT content but increased palmitic, stearic, and oleic acids in pre-type II cells. Furthermore, hypertriglyceridemic apolipoprotein E knockout mice contained significantly greater levels of DSPtdCho content in alveolar lavage and CCT activity compared with either LDL receptor knockout mice or wild-type controls that have normal serum triglycerides. Thus the nutritional or genetic modulation of serum VLDL-triglycerides provides specific fatty acids that stimulate PtdCho synthesis and CCT activity thereby increasing surfactant content.

The argument for increasing selenium intake.

Rayman MP, Rayman MP. *Proc Nutr Soc* 2002;61:203-215.

The essential trace mineral, Se, is of fundamental importance to human health. As a constituent of selenoproteins it plays both structural and enzymic roles, in the latter context being best known as an antioxidant and catalyst for the production of active thyroid hormone. While Se-deficiency diseases have been recognised for some time, evidence is mounting that less-overt deficiency can also cause adverse health effects and furthermore, that supra-nutritional levels of Se may give additional protection from disease. In the context of these effects, low or diminishing Se status in some parts of the world, notably in some European countries such as the UK, is giving cause for concern. While deficiency has an adverse effect on immunocompetence, Se supplementation appears to enhance the immune response. Se appears to be a key nutrient in counteracting certain viral infections; thus, in a Se-deficient host the benign coxsackie virus becomes virulent, causing heart damage, the influenza virus causes more serious lung pathology and HIV infection progresses more rapidly to AIDS. Long recognised as essential for successful animal reproduction, Se is required for human sperm maturation and sperm motility and may reduce the risk of miscarriage. Deficiency has been linked to adverse mood states. Findings have been equivocal in linking Se to cardiovascular disease risk, although other conditions involving oxidative stress and inflammation have shown some association with Se status. There is growing evidence that higher Se intakes are associated with reduced cancer risk. While persuasive evidence already exists to suggest that additional Se would be beneficial in some health conditions, results from intervention trials underway or planned have the potential to reinforce or refute the argument for increasing Se intake.

The effect of N-acetylcysteine supplementation upon viral load, CD4, CD8, total lymphocyte count and hematocrit in individuals undergoing antiretroviral treatment.

Spada C, Treitinger A, Reis M, et al. *Clin Chem Lab Med* 2002;40:452-455.

Individuals infected with the human immunodeficiency virus (HIV-1) present with decreased CD4, a progressive increase in viral load, compromised cell immune defense, and hematologic alterations. The aim of this study was to assess the serum viral load, CD4, CD8, lymphocyte count and hematocrit at the beginning of antiretroviral therapy in individuals who were supplemented with N-acetylcysteine (NAC). Twenty volunteers participated in this double-blind, placebo-controlled 180-day study. Ten participants received 600 mg of NAC per day (NAC group) and the other ten serving as a control group received placebo. The above mentioned parameters were determined before treatment, and after 60, 120 and 180 days. In NAC-treated patients hematocrit remained stable and an increase in CD4 cell count took place earlier than that in the control group.