

**Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high-fat meal.**

Plotnick GD, Corretti MC, Vogel RA.

*JAMA* 1997;278:1682-1686.

Context.—Much has been written about the potential role of antioxidants in the prevention of atherosclerosis.

Objective.—To assess the short-term effect of a single high-fat meal with and without pretreatment with antioxidant vitamins on endothelial function in healthy, normocholesterolemic subjects.

Design.—Observer-blinded randomized trial.

Setting.—University hospital.

Participants.—Twenty healthy, normocholesterolemic (total and low-density lipoprotein cholesterol <5.2 mmol/L and <3.4 mmol/L [ $<200$  mg/dL and  $<130$  mg/dL], respectively), male (7) and female (13) hospital employee volunteers, aged 24 to 54 years.

Intervention.—Three randomly administered breakfasts: (1) a high-fat meal (3766 J [900 calories], 50 g of fat); (2) a low-fat meal (3766 J [900 calories], 0 g of fat); and (3) a high-fat meal and pretreatment with oral administration of vitamins C (1 g) and E (800 IU) (high-fat meal with vitamins). A subgroup of 10 subjects also ate the low-fat meal with the same vitamin pretreatment (low-fat meal with vitamins).

Main Outcome Measure.—High-resolution ultrasound assessed flow-mediated (endothelium-dependent) brachial artery vasodilation measured as percent diameter change before and hourly for 6 hours following each meal.

Results.—Flow-mediated vasodilation fell from a mean SD of  $20\% \pm 8\%$  before to  $12\% \pm 6\%$ ,  $10\% \pm 6\%$ , and  $8\% \pm 9\%$  at 2, 3, and 4 hours, respectively, after the high-fat meal ( $P < .001$ ). No significant changes in flow-mediated vasodilation occurred after the low-fat meal, high-fat meal with vitamins, or low-fat meal with vitamins. The change in flow-mediated vasodilation after the low-fat and high-fat meals correlated inversely with the 2-hour postprandial change in triglyceride levels ( $r = -0.54$ ;  $P < .001$ ).

Conclusion.—A single high-fat meal transiently reduces endothelial function for up to 4 hours in healthy, normocholesterolemic subjects, probably through the accumulation of triglyceride-rich lipoproteins. This decrease is blocked by pretreatment with antioxidant vitamins C and E, suggesting an oxidative mechanism.

### **Dietary fat intake and the risk of coronary heart disease in women.**

Hu FB, Stampfer MJ, Manson JE, et al.  
*N Engl J Med*  
1997;337:1491-9.

**Background.** The relation between dietary intake of specific types of fat, particularly trans unsaturated fat, and the risk of coronary disease remains unclear. We therefore studied this relation in women enrolled in the Nurses' Health Study.

**Methods.** We prospectively studied 80,082 women who were 34 to 59 years of age and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes in 1980. Information on diet was obtained at base line and updated during follow-up by means of validated questionnaires. During 14 years of follow-up, we documented 939 cases of nonfatal myocardial infarction or death from coronary heart disease. Multivariate analyses included age, smoking status, total energy intake, dietary cholesterol intake, percentages of energy obtained from protein and specific types of fat, and other risk factors.

**Results.** Each increase of 5 percent of energy intake from saturated fat, as compared with equivalent energy intake from carbohydrates, was associated with a 17 percent increase in the risk of coronary disease (relative risk, 1.17; 95 percent confidence interval, 0.97 to 1.41;  $P = 0.10$ ). As compared with equivalent energy from carbohydrates, the relative risk for a 2 percent increment in energy intake from trans unsaturated fat was 1.93 (95 percent confidence interval, 1.43 to 2.61;  $P < 0.001$ ); that for a 5 percent increment in energy from monounsaturated fat was 0.81 (95 percent confidence interval, 0.65 to 1.00;  $P = 0.05$ ); and that for a 5 percent increment in energy from polyunsaturated fat was 0.62 (95 percent confidence interval, 0.46 to 0.85;  $P = 0.003$ ). Total fat intake was not significantly related to the risk of coronary disease (for a 5 percent increase in energy from fat, the relative risk was 1.02; 95 percent confidence interval, 0.97 to 1.07;  $P = 0.55$ ). We estimated that the replacement of 5 percent of energy from saturated fat with energy from unsaturated fats would reduce risk by 42 percent (95 percent confidence interval, 23 to 56;  $P < 0.001$ ) and that the replacement of 2 percent of energy from trans fat with energy from unhydrogenated, unsaturated fats would reduce risk by 53 percent (95 percent confidence interval, 34 to 67;  $P < 0.001$ ).

**Conclusions.** Our findings suggest that replacing saturated and trans unsaturated fats with unhydrogenated monounsaturated and polyunsaturated fats is more effective in preventing coronary heart disease in women than reducing overall fat intake.

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### **A placebo-controlled, double-blind, randomized trial of an extract of ginkgo biloba for dementia.**

Le Bars PL, Katz MM, Berman N, et al. *JAMA*. 1997;278:1327-1332.

CONTEXT.—EGb 761 is a particular extract of Ginkgo biloba used in Europe to alleviate symptoms associated with numerous cognitive disorders. Its use in dementias is based on positive results from only a few controlled clinical trials, most of which did not include standard assessments of cognition and behavior. OBJECTIVE.—To assess the efficacy and safety of EGb in Alzheimer disease and multi-infarct dementia. DESIGN.—A 52-week, randomized double-blind, placebo-controlled, parallel-group, multicenter study. PATIENTS.—Mildly to severely demented outpatients with Alzheimer disease or multi-infarct dementia, without other significant medical conditions. INTERVENTION.—Patients assigned randomly to treatment with EGb (120 mg/d) or placebo. Safety, compliance, and drug dispensation were monitored every 3 months with complete outcome evaluation at 12, 26, and 52 weeks. PRIMARY OUTCOME MEASURES.—Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Geriatric Evaluation by Relative's Rating Instrument (GERRI), and Clinical Global Impression of Change (CGIC). RESULTS.—From 309 patients included in an intent-to-treat analysis, 202 provided evaluable data for the 52-week end point analysis. In the intent-to-treat analysis, the EGb group had an ADAS-Cog score 1.4 points better than the placebo group ( $P=.04$ ) and a GERRI score 0.14 points better than the placebo group ( $P=.004$ ). The same patterns were observed with the evaluable data set in which 27% of patients treated with EGb achieved at least a 4-point improvement on the ADAS-Cog, compared with 14% taking placebo ( $P=.005$ ); on the GERRI, 37% were considered improved with EGb, compared with 23% taking placebo ( $P=.003$ ). No difference was seen in the CGIC. Regarding the safety profile of EGb, no significant differences compared with placebo were observed in the number of patients reporting adverse events or in the incidence and severity of these events. CONCLUSIONS.—EGb was safe and appears capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients for 6 months to 1 year. Although modest, the changes induced by EGb were objectively measured by the ADAS-Cog and were of sufficient magnitude to be recognized by the caregivers in the GERRI.

**Vitamin E  
supplementation in elderly  
lowers the oxidation rate  
of linoleic acid in LDL.**

de Waart FG, Moser U, Kok  
FJ. *Atherosclerosis*  
1997;133:255-263.

Oxidation of LDL-linoleic acid (LDL-LA), a major substrate for lipid peroxidation, may be counteracted by the antioxidant vitamin E. In a 3-month randomized double-blind placebo-controlled trial in 83 apparently healthy Dutch elderly, aged 67-85 years, the direct protective effect of 100 IU vitamin E on the rate of oxidized LDL-LA was studied. The oxidation of LDL-LA was measured by its disappearance after a 5-h in vitro Cu-oxidation of LDL isolated from 1 ml plasma. In the vitamin E group, the decrease in oxidized LDL LA of 10.4, ( $p < 0.05$ ) was significantly different ( $p < 0.05$ ) from the smaller 4.6%  $p < 0.01$  decrease in the control group. Moreover, within the vitamin E group the decrease was even more marked over tertiles of alpha-tocopherol to LDL-LA ratio with a significant difference in decrease ( $p < 0.05$ ) from the lowest compared to the highest tertile of, respectively, 18.4% [-24; -2%] (median and range) and 2.0% [-16; 34%]. In conclusion, supplementation with 100 IU vitamin E in elderly is beneficial in lowering the rate of oxidation of LDL LA. The protective effect of vitamin E might best be monitored by using the ratio of alpha-tocopherol to LDL-LA as this reflects the degree of alpha-tocopherol available to protect the amount of LDL-LA present.

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### **Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial.**

Girodon F, Lombard M, Galan P, et al. *Ann Nutr Metab* 1997;41:98-107.

To determine the impact of a trace element and vitamin supplementation on infectious morbidity, a double-blind controlled trial was performed on 81 elderly subjects in a geriatric center during a 2-year period. Subjects were randomly assigned to one of four treatment groups, and received daily: placebo; trace elements/zinc 20 mg; selenium 100 micrograms); vitamins (vitamin C 120 mg; beta-carotene 6 mg; alpha-tocopherol 15 mg); or a combination of trace elements and vitamins at equal doses. (1) Before supplementation, low serum values in vitamin C, folate, zinc and selenium were observed in more than two thirds of the patients. (2) After 6 months of supplementation, a significant increase in vitamin and trace element serum levels was obtained in the corresponding treatment groups: a plateau was then observed for the whole study. (3) Subjects who received trace elements (zinc and selenium) alone or associated with vitamins had significantly less infectious events during the 2 years of supplementation. These results indicate that supplementation with low doses of vitamins and trace elements is able to rapidly correct corresponding deficiencies in the institutionalized elderly. Moreover, zinc and selenium reduced infectious events.

**Effect of a two-year supplementation with low doses of antioxidant vitamins and/or minerals in elderly subjects on levels of nutrients and antioxidant defense parameters.**

Girodon F, Blache D, Monget AL, et al. *J Am Coll Nutr* 1997;16:357-365.

**BACKGROUND:** Eighty-one elderly hospitalized subjects (> 65 years) were recruited for a double-blind placebo-controlled study to examine low dose supplementation of antioxidant vitamins and minerals on biological and functional parameters of free radical metabolism. Subjects were randomly assigned to one of the four treatment groups, daily receiving for 2 years: placebo group; mineral group: 20 mg zinc, 100 micrograms selenium; vitamin group: 120 mg vitamin C (Vit C), 6 mg beta-carotene (beta CA), 15 mg vitamin E (Vit E); mineral and vitamin group: Zn 20 mg, Se 100 micrograms, Vit C 120 mg, beta CA 6 mg, Vit E 15 mg. **RESULTS:** Fifty-seven subjects completed the study. A large frequency of Vit C, Zn and Se deficiencies were observed at baseline. As early as 6 months of treatment, a significant increase in vitamin and mineral serum levels was observed in the corresponding groups. The increases ranged from 1.1-4.0 fold depending on the nutrient. Antioxidant defense, studied in vitro with a test using red blood cells in presence of 2,2'-azo-bis (2-amidinopropane) by hydrochloride, showed an increase of cell resistance in patients receiving vitamins ( $p = 0.002$ ); it was positively correlated with serum Vit C ( $p < 0.0001$ ), alpha-tocopherol/cholesterol ( $p = 0.06$ ), beta CA ( $p = 0.0014$ ), serum Cu and Se ( $p < 0.05$ ). Moreover, red blood cell antioxidant defense was reduced in elderly compared with young control subjects (50% hemolysis time: 69 +/- 14 mn and 109 +/- 12 mn, respectively). Erythrocyte glutathione peroxidase activity was enhanced in groups receiving minerals, whereas no significant change was observed for other indicators of oxidative stress (erythrocyte superoxide dismutase activity, thiobarbituric acid-reactive substances, total glutathione, reduced and oxidized forms). **DISCUSSION:** Our results provide experimental evidence that a low dose supplementation with vitamins and minerals was able to normalize biological nutrient status as early as 6 months of treatment. In addition, our data indicate that antioxidant defense in elderly subjects was improved with low doses of vit C, vit E and beta CA as studied by means of a functional test utilizing red blood cells challenged in vitro with free radicals.

**Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: results of a double-blind, randomised trial.**

Smyth JF, Bowman A, Perren T, et al. *Ann Oncol* 1997;8:569-573.

**BACKGROUND:** Early clinical trials have suggested that glutathione (GSH) offers protection from the toxic effects of cisplatin. **PATIENTS AND METHODS:** One hundred fifty-one patients with ovarian cancer (stage I-IV) were evaluated in a clinical trial of cisplatin (CDDP) +/- glutathione (GSH). The objective was to determine whether GSH would enhance the feasibility of giving six cycles of CDDP at 100 mg/m<sup>2</sup> without dose reduction due to toxicity. **RESULTS:** When considering the proportion of patients receiving six courses of CDDP at any dose, GSH produced a significant advantage over control—58% versus 39%, (P = 0.04). For these patients there was a significant difference between the reduction in creatinine clearance for GSH treated patients compared with control—74% versus 62% (P = 0.006). Quality of life scores demonstrated that for patients receiving GSH there was a statistically significant improvement in depression, emesis, peripheral neurotoxicity, hair loss, shortness of breath and difficulty concentrating. As an indication of overall activity, these patients were statistically significantly more able to undertake housekeeping and shopping. Clinically assessed response to treatment demonstrated a trend towards a better outcome in the GSH group (73% versus 62%) but this was not statistically significant (P = 0.25). **CONCLUSIONS:** The results demonstrate that adding GSH to CDDP allows more cycles of CDDP treatment to be administered because less toxicity is observed and the patient's quality of life is improved.

**Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment.**

De Flora S, Grassi C, Carati L. *Eur Respir J* 1997;10:1535-1541.

N-acetylcysteine (NAC), an analogue and precursor of reduced glutathione, has been in clinical use for more than 30 yrs as a mucolytic drug. It has also been proposed for and/or used in the therapy and/or prevention of several respiratory diseases and of diseases involving an oxidative stress, in general. The objective of the present study was to evaluate the effect of long-term treatment with NAC on influenza and influenza-like episodes. A total of 262 subjects of both sexes (78%  $\geq$  65 yrs, and 62% suffering from nonrespiratory chronic degenerative diseases) were enrolled in a randomized, double-blind trial involving 20 Italian Centres. They were randomized to receive either placebo or NAC tablets (600 mg) twice daily for 6 months. Patients suffering from chronic respiratory diseases were not eligible, to avoid possible confounding by an effect of NAC on respiratory symptoms. NAC treatment was well tolerated and resulted in a significant decrease in the frequency of influenza-like episodes, severity, and length of time confined to bed. Both local and systemic symptoms were sharply and significantly reduced in the NAC group. Frequency of seroconversion towards A/H1N1 Singapore 6/86 influenza virus was similar in the two groups, but only 25% of virus-infected subjects under NAC treatment developed a symptomatic form, versus 79% in the placebo group. Evaluation of cell-mediated immunity showed a progressive, significant shift from anergy to normoergy following NAC treatment. Administration of N-acetylcysteine during the winter, thus, appears to provide a significant attenuation of influenza and influenza-like episodes, especially in elderly high-risk individuals. N-acetylcysteine did not prevent A/H1N1 virus influenza infection but significantly reduced the incidence of clinically apparent disease.

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**Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients.**

Velussi M, Cernigoi AM, De Monte A, et al. *J Hepatol* 1997;26:871-879.

**BACKGROUND/AIMS:** Several studies have demonstrated that diabetic patients with cirrhosis require insulin treatment because of insulin resistance. As chronic alcoholic liver damage is partly due to the lipoperoxidation of hepatic cell membranes, anti-oxidizing agents may be useful in treating or preventing damage due to free radicals. The aim of this study was to ascertain whether long-term treatment with silymarin is effective in reducing lipoperoxidation and insulin resistance in diabetic patients with cirrhosis. **METHODS:** A 12-month open, controlled study was conducted in two well-matched groups of insulin-treated diabetics with alcoholic cirrhosis. One group (n=30) received 600 mg silymarin per day plus standard therapy, while the control group (n=30) received standard therapy alone. The efficacy parameters, measured regularly during the study, included fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria levels, glycosylated hemoglobin (HbA1c) and malondialdehyde levels. **RESULTS:** There was a significant decrease ( $p<0.01$ ) in fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria and HbA1c levels already after 4 months of treatment in the silymarin group. In addition, there was a significant decrease ( $p<0.01$ ) in fasting insulin levels and mean exogenous insulin requirements in the treated group, while the untreated group showed a significant increase ( $p<0.05$ ) in fasting insulin levels and a stabilized insulin need. These findings are consistent with the significant decrease ( $p<0.01$ ) in basal and glucagon-stimulated C-peptide levels in the treated group and the significant increase in both parameters in the control group. Another interesting finding was the significant decrease ( $p<0.01$ ) in malondialdehyde/levels observed in the treated group. **CONCLUSIONS:** These results show that treatment with silymarin may reduce the lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and the need for exogenous insulin administration.

**Effect of oral coenzyme Q10 supplementation on the oxidation resistance of human VLDL+LDL fraction: absorption and antioxidative properties of oil and granule-based preparations.**

Kaikkonen J, Nyssonen K, Porkkala-Sarataho E, et al. *Free Radic Biol Med* 1997;22:1195-1202.

Coenzyme Q10 (Q10) is supposed to be an important endogenous lipid-soluble antioxidant. We studied 60 healthy 46 +/- 7 (mean +/- SD)-year-old smoking men. They were randomized into three groups to receive oil-based or granular Q10 (90 mg/d) or placebo for 2 months. Oil-based capsule elevated Q10 in plasma by 178% and in VLDL+LDL fraction by 160%. The granular preparation increased Q10 in plasma by 168% and in VLDL+LDL by 127%. However, the 2-month Q10 supplementation did not increase the oxidation resistance of VLDL+LDL fraction, as assessed by copper induced VLDL+LDL oxidation, haemin+H(2)O(2)-induced VLDL+LDL oxidation, total antioxidative capacity of LDL, and plasma malondialdehyde measurements. The first and the last dose was used to carry out a 12 h pharmacokinetic study (five subjects per group), which indicated that only a small part of supplemented Q10 was absorbed to the circulation in 12 h and that the absorption varied extensively between subjects. Our results suggest that at least among smoking men, 90 mg of orally supplemented Q10 daily does not increase the oxidation resistance of VLDL+LDL. Bioavailability of both the granular and the oil-based Q10 preparation was similar during the long-term supplementation, but one dose of 30 mg had only a marginal effect on the plasma levels of Q10.

**Antioxidants enhance the cytotoxicity of chemotherapeutic agents in colorectal cancer: A p53-independent induction of p21<sup>WAF1/CIP1</sup> via C/EBPbeta.**

Chinery R, Brockman JA, Peeler MO, et al. *Nature Med* 1997;3:1233-1241.

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States. Five-fluorouracil (5FU) remains the single most effective treatment for advanced disease, despite a response rate of only 20%. Herein, we show that the antioxidants pyrrolidinedithiocarbamate and vitamin E induce apoptosis in CRC cells. This effect is mediated by induction of p21<sup>WAF1/CIP1</sup>, a powerful inhibitor of the cell cycle, through a mechanism involving C/EBPbeta (a member of the CCAAT/enhancer binding protein family of transcription factors), independent of p53. Antioxidants significantly enhance CRC tumor growth inhibition by cytotoxic chemotherapy in vitro (5FU and doxorubicin) and in vivo (5FU). Thus, chemotherapeutic agents administered in the presence of antioxidants may provide a novel therapy for colorectal cancer.

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### **Mechanisms of growth inhibition of human lung cancer cell line, PC-9, by tea polyphenols.**

Okabe S, Suganuma M, Hayashi M, et al. *Jpn J Cancer Res* 1997;88:639-643.

(-)-Epigallocatechin gallate (EGCG), the main constituent of green tea, and green tea extract show growth inhibition of various cancer cell lines, such as lung, mammary, and stomach. We studied how tea polyphenols induce growth inhibition of cancer cells. Since green tea extract contains various tea polyphenols, such as EGCG, (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epicatechin (EC), the inhibitory potential of each tea polyphenol on the growth of a human lung cancer cell line, PC-9 cells, was first examined. EGC and ECG inhibited the growth of PC-9 cells as potently as did EGCG, but EC did not show significant growth inhibition. The mechanism of growth inhibition by EGCG was studied in relation to cell cycle regulation. Flow cytometric analysis revealed that treatment with 50 microM and 100 microM EGCG increased the percentages of cells in the G2-M phase from 13.8% to 15.6% and 24.1%, respectively. The DNA histogram after treatment with 100 microM EGCG was similar to that after treatment with genistein, suggesting that EGCG induces G2-M arrest in PC-9 cells. Moreover, we found by microautoradiography that [3H]EGCG was incorporated into the cytosol, as well as the nuclei. These results provide new insights into the mechanisms of action of EGCG and green tea extract as cancer-preventive agents in humans.

### **The effects of intravenous antioxidants in patients with septic shock.**

Galley HF, Howdle PD,  
Walker BE, Webster NR.  
*Free Radic Biol Med*  
1997;23:768-774.

Oxidative stress is implicated in septic shock. We investigated the effect of intravenous antioxidant therapy on antioxidant status, lipid peroxidation, hemodynamics and nitrite in patients with septic shock. Thirty patients randomly received either antioxidants (n-acetylcysteine 150 mg/kg for 30 min then 20 mg/kg/h plus bolus doses of 1 g ascorbic acid and 400 mg alpha-tocopherol) or 5% dextrose. Basal vitamin C was low and redox-reactive iron was elevated in all patients. In the 16 patients receiving antioxidants, vitamin C increased ( $p = .0002$ ) but total antioxidant capacity was unaffected. Lipid peroxides were elevated in all patients but did not increase further in the patients receiving antioxidants. Plasma total nitrite also increased ( $p = .007$ ) in the antioxidant group. Heart rate increased in patients receiving antioxidants at 60 min ( $p = .018$ ) and 120 min ( $p = .004$ ). Cardiac index also increased at 60 min ( $p = .007$ ) and 120 min ( $p = .05$ ). Systemic vascular resistance index decreased at 120 min in the antioxidant treated patients ( $p = .003$ ). The effect of antioxidants on hemodynamic variables has not previously been reported. Antioxidant administration may be a useful adjunct to conventional approaches in the management of septic shock.

**A pilot study of the effects of d-alpha-tocopherol on hepatic stellate cell activation in chronic hepatitis C.**

Houglum K, Venkataramani A, Lyche K, Chojkier M.  
*Gastroenterology*  
1997;113:1069-1073.

**BACKGROUND & AIMS:** Oxidative stress mediates activation and stimulates collagen production of cultured hepatic stellate (Ito) cells. The aim of this study was to assess whether oxidative stress contributes to hepatic fibrogenesis in chronic hepatitis C. **METHODS:** In liver biopsy specimens of patients with chronic hepatitis C, the following fibrogenesis cascade was analyzed: (1) oxidative stress, determined by the presence of malondialdehyde protein adducts; (2) activation of stellate cells as indicated by their expression of alpha-smooth muscle actin; (3) stimulation of c-myc expression in stellate cells, a critical step in the activation of these cells; and (4) induction of collagen gene expression as detected by in situ hybridization. **RESULTS:** Treatment with d-alpha-tocopherol (1200 IU/day for 8 weeks) in 6 of these patients, who were refractory to interferon therapy, prevented the fibrogenesis cascade observed before antioxidant treatment. In addition, d-alpha-tocopherol treatment significantly decreased the carbonyl modifications of plasma proteins, a sensitive index of oxidative stress. However, 8 weeks of d-alpha-tocopherol treatment did not significantly affect serum alanine aminotransferase levels, hepatitis C virus titers, or histological degree of hepatocellular inflammation or fibrosis. **CONCLUSIONS:** These data suggest that enhanced oxidative stress initiates a fibrogenesis cascade in the liver of patients with chronic hepatitis C.

**Antioxidant nutrient supplementation reduces the susceptibility of low density lipoprotein to oxidation in patients with coronary artery disease.**

Mosca L, Rubenfire M, Mandel C, et al. *J Am Coll Cardiol* 1997;30:392-399.

**OBJECTIVE:** This study sought to determine the effect of antioxidant supplementation on the susceptibility of low density lipoprotein (LDL) to oxidation in patients with established cardiovascular disease (CVD). **BACKGROUND:** Data are inconsistent regarding the role of antioxidant nutrients in the prevention of CVD. **METHODS:** The study design was a 12-week, double-blind, placebo-controlled clinical trial. Patients with CVD (n = 45) were randomized to 1) placebo control; 2) 400 IU of vitamin E, 500 mg of vitamin C, 12 mg of beta-carotene (mid-dose); or 3) 800 IU of vitamin E, 1,000 mg of vitamin C, 24 mg of beta-carotene (high dose) daily. Reduced susceptibility of LDL to oxidation was estimated by an increase in lag phase (minutes). Baseline and 6- and 12-week measurements of lipoproteins and lag phase were obtained. Plasma levels of antioxidants were measured at baseline and 12 weeks. **RESULTS:** Concentrations of alpha-tocopherol, vitamin C and beta-carotene significantly increased in the mid- and high dose groups during the trial. Lag phase significantly increased from baseline (190.1 +/- 63.8 min [mean +/- SD]) to 12 weeks (391.1 +/- 153.0 min) in the high dose group (p < 0.01). A nonsignificant increase in lag phase in the mid-dose group was observed during the same time interval. A dose response was found for mean percent change from baseline to 12 weeks for lag phase for the placebo, mid- and high dose groups (p = 0.004 for trend). **CONCLUSIONS:** A high dose combination of antioxidant nutrients reduces the susceptibility of LDL to oxidation in patients with CVD and may be useful in secondary prevention.

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**Saccharomyces boulardii prevents diarrhea in critically ill tube-fed patients. A multicenter, randomized, double-blind placebo-controlled trial.**

Bleichner G, Blehaut H, Mentec H, Moyses D.  
*Intensive Care Med*  
1997;23:517-523.

**OBJECTIVE:** To assess the preventive effect of *Saccharomyces boulardii* on diarrhea in critically ill tube-fed patients and to evaluate risk factors for diarrhea. **DESIGN:** Prospective, multicenter, randomized, double-blind placebo-controlled study. **SETTING:** Eleven intensive care units in teaching and general hospitals. **PATIENTS:** Critically ill patients whose need for enteral nutrition was expected to exceed 6 days. **INTERVENTION:** *S. boulardii* 500 mg four times a day versus placebo. **MEASUREMENTS AND RESULTS:** Diarrhea was defined by a semiquantitative score based on the volume and consistency of stools. A total of 128 patients were studied, 64 in each group. Treatment with *S. boulardii* reduced the mean percentage of days with diarrhea per feeding days from 18.9 to 14.2% [odds ratio (OR) = 0.67, 95% confidence interval (CI) = 0.50-0.90, P = 0.0069]. In the control group, nine risk factors were significantly associated with diarrhea: nonsterile administration of nutrients in open containers, previous suspension of oral feeding, malnutrition, hypoalbuminemia, sepsis syndrome, multiple organ failure, presence of an infection site, fever or hypothermia, and use of antibiotics. Five independent factors were associated with diarrhea in a multivariate analysis: fever or hypothermia, malnutrition, hypoalbuminemia, previous suspension of oral feeding, and presence of an infection site. After adjustment for these factors, the preventive effect of *S. boulardii* on diarrhea was even more significant (OR = 0.61, 95% CI = 0.44-0.84, P < 0.0023). **CONCLUSIONS:** *S. boulardii* prevents diarrhea in critically ill tube-fed patients, especially in patients with risk factors for diarrhea.

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### **Chemoprevention of oral leukoplakia with vitamin A and beta carotene: an assessment.**

Sankaranarayanan R,  
Mathew B, Varghese C, et al.  
*Oral Oncol* 1997;33:231-236.

We conducted a double-blind placebo-controlled trial to evaluate the chemopreventive potential of either vitamin A alone or beta carotene alone in subjects with oral leukoplakia in Kerala, India. We randomised 160 fishermen and women with oral precancerous lesions to receive oral vitamin A (retinyl acetate 300,000 IU/week x 12 months, n = 50), or beta carotene (360 mg/week x 12 months, n = 55), or placebo (n = 55). Blood, saliva and urine samples were collected at baseline and at exit to study serum micronutrients and mutagenicity assays. Biopsies of the mucosal lesions at entry were performed for histopathological exclusion of malignancy. The subjects were examined once every 2 months to establish clinical response of lesions and toxicity, if any. The results are based on 43 complaint subjects on placebo, 42 on vitamin A and 46 on beta carotene. The complete regression rates were: 10% in the placebo arm, 52% with vitamin A and 33% with beta carotene ( $P < 0.0001$ ). Homogeneous leukoplakias and smaller lesions responded better than non-homogeneous and larger lesions. No major toxicities were observed. Half of the responders with beta carotene and two thirds with vitamin A relapsed after stopping supplementation. Serum beta carotene concentration increased substantially with beta carotene administration while with vitamin A supplementation there was no change in serum retinol levels. In the vitamin A treated group there was a significant decrease in serum alpha tocopherol. Vitamin A administration resulted in a significant remission of oral leukoplakia without any side effects of prolonged vitamin A supplementation. The results of this study, as well as those from previous studies, appear to provide strong supporting evidence to justify long term trials with vitamin A in subjects with high-risk leukoplakias with oral cancer as an endpoint.

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### **Lipoic acid increases de novo synthesis of cellular glutathione by improving cystine utilization.**

Han D, Handelman G, Marcocci L, et al. *Biofactors* 1997;6:321-338.

Lipoic acid (thiotic acid) is being used as a dietary supplement, and as a therapeutic agent, and is reported to have beneficial effects in disorders associated with oxidative stress, but its mechanism of action remains unclear. We present evidence that lipoic acid induces a substantial increase in cellular reduced glutathione in cultured human Jurkat T cells human erythrocytes, C6 glial cells, NB41A3 neuroblastoma cells, and peripheral blood lymphocytes. The effect depends on metabolic reduction of lipoic acid to dihydrolipoic acid. Dihydrolipoic acid is released into the culture medium where it reduces cystine. Cystine thus formed is readily taken up by the neutral amino acid transport system and utilized for glutathione synthesis. By this mechanism lipoic acid enables cystine to bypass the xc- transport system, which is weakly expressed in lymphocytes and inhibited by glutamate. Thereby lipoic acid enables the key enzyme of glutathione synthesis, gamma-glutamylcysteine synthetase, which is regulated by uptake-limited cysteine supply, to work at optimum conditions. Flow cytometric analysis of freshly prepared human peripheral blood lymphocytes, using monobromobimane labeling of cellular thiols, reveals that lipoic acid acts mainly to normalize a subpopulation of cells severely compromised in thiol status rather than to increase thiol content beyond physiological levels. Hence lipoic acid may have clinical relevance in restoration of severely glutathione deficient cells.

### **The relationship between selenium and immunity in large bowel cancer.**

Yu B, Wang M, Li D. *Chung Hua Wai Ko Tsa Chih* 1996;34:50-53.

44 patients with large bowel cancer were randomly divided into two groups, therapeutic and control group. The level of serum selenium, T lymphocyte subsets consisted of CD3, CD4, CD8, CD4/CD8, NK and LAK cell activity were measured preoperation and postoperation. Simultaneously se content in tumor and normal tissue of the large bowel were measured in 35 cases. Serum se level ( $0.81 \pm 0.14$  umol/L) was lowered in patients with large bowel cancer and increased significantly after se supplementation in the therapeutic group ( $P < 0.01$ ). It was significantly different from that of the control group ( $P < 0.01$ ), CD3, CD4, CD4/CD8, NK and LAK cell activity were obviously increased postoperatively in the therapeutic group and significantly different from those of the control group. The results suggest that supplement of Se can promote cell-mediated immunity in humans. In addition, Se can promote cell-mediated immunity in humans. The Se level of  $22.13 \pm 1.76$  umol/g in tumor was significantly lower than that of  $24.30 \pm 1.96$  umol/g in normal mucosa in case of large bowel cancer ( $P < 0.01$ ). This indicates that there may be a close relationship between low Se level and the carcinogenesis of the colon and rectum.

### **A trial of antioxidants N-acetylcysteine and procysteine in ARDS. The Antioxidant in ARDS Study Group.**

Bernard GR, Wheeler AP, Arons MM, et al. *Chest* 1997;112:164-172.

**OBJECTIVE:** To determine the levels of glutathione and cysteine in patients with ARDS and examine the effect of treatment with N-acetylcysteine (NAC) and L-2-oxothiazolidine-4-carboxylate (Procysteine; Clintec Technologies Inc; Chicago [OTZ]) on these levels and on common physiologic abnormalities, and organ dysfunction associated with ARDS. **DESIGN:** Randomized, double-blind, placebo-controlled, prospective clinical trial. **SETTING:** ICUs in five clinical centers in the United States and Canada. **PATIENTS:** Patients meeting a predetermined definition of ARDS and requiring mechanical ventilation. **INTERVENTION:** Standard care for ARDS and I.V. infusion, every 8 h for 10 days, of one of the following: NAC (70 mg/kg, n=14), OTZ (63 mg/kg, n=17), or placebo (n=15). **MAIN RESULTS:** Both antioxidants effectively repleted RBC glutathione gradually over the 10-day treatment period (47% and 49% increases from baseline values for NAC and OTZ, respectively). There was no difference in mortality among groups (placebo, 40%; NAC, 36%; OTZ, 35%). However, the number of days of acute lung injury was decreased and there was also a significant increase in cardiac index in both treatment groups (NAC/OTZ [+]14%; placebo [-]6%). **CONCLUSIONS:** Our findings suggest that repletion of glutathione may safely be accomplished with NAC or OTZ in patients with acute lung injury/ARDS. Such treatment may shorten the duration of acute lung injury, but larger studies are needed to confirm this.

### **Elevated blood copper/zinc ratios in assaultive young males.**

Walsh WJ, Isaacson HR, Rehman F, Hall A. *Physiol Behav* 1997;62:327-329.

In research conducted over the past 20 years, we have observed abnormal trace-metal concentrations, including elevated serum copper and depressed plasma zinc, in blood samples collected from violence-prone individuals. The purpose of the study reported here was to test the validity of our observation that assaultive young males have elevated blood copper/zinc (Cu/Zn) ratios when compared to a control group of young males with no history of assaultive behavior. All male patients between the ages of 3 years and 20 years who made a first visit to the outpatient Pfeiffer Treatment Center in Naperville, Ill., during a two-month period were evaluated. Based on interviews with patients and their families and application of a standardized behavior scale, 135 assaultive young males and 18 controls with no history of assaultive behavior were identified. Blood samples were collected from test subjects and controls and analyzed for serum copper and plasma zinc concentrations by an independent laboratory using atomic absorption methods. The median Cu/Zn ratio for the assaultive subjects was 1.40 compared to 1.02 for controls, a statistically significant difference ( $t = 5.94$ ;  $p < 0.01$ ).

# Abstracts

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## Recently Published Abstracts

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### **Combination of low-dose niacin and pravastatin improves the lipid profile in diabetic patients without compromising glycemic control.**

Gardner SF, Marx MA, White LM, et al. *Ann Pharmacother* 1997;31:677-682.

**OBJECTIVE:** To determine the efficacy and tolerability of the addition of low-dose niacin (1.5 g/d) in a diabetic hypercholesterolemic population who were unable to attain desired lipid control with low-dose (20 mg) pravastatin monotherapy. **RESEARCH DESIGN AND METHODS:** This was a prospective, open-label study conducted over a 14-week period. Twenty-three diabetic patients with low-density lipoprotein (LDL) cholesterol concentrations of at least 150 mg/dL after dietary therapy were recruited from the outpatient diabetes clinic of a university teaching hospital. After 4 weeks of dietary stabilization and baseline determination of the lipid profile and glycemic control, patients received pravastatin 20 mg once daily for 4 weeks. Laboratory parameters were reassessed and niacin was added to the regimen in qualifying patients. Over 2 weeks, patients' regimens were titrated to a maximal dosage of 500 mg tid. Patients continued to receive the combination regimen for 4 weeks and were reassessed. **MEASUREMENTS AND MAIN RESULTS:** Sixteen patients (14 non-insulin-dependent diabetes mellitus, 2 insulin-dependent diabetes mellitus) completed the study. Mean fasting blood sugar and fructosamine concentrations were unchanged throughout the study. Five patients required minor alterations (3 increased, 2 decreased) in their hypoglycemic regimens during the study. The addition of low-dose niacin to pravastatin therapy resulted in a significant lowering of LDL cholesterol compared with pravastatin monotherapy. **CONCLUSIONS:** Low-dose niacin is a promising addition to hydroxymethylglutaryl-coenzyme A reductase inhibitor therapy in the treatment of hypercholesterolemia in patients with diabetes mellitus.

### **Effects of kawain and dihydromethysticin on field potential changes in the hippocampus.**

Walden J, von Wegerer J, Winter U, et al. *Prog Neuropsychopharmacol Biol Psychiatry* 1997;21:697-706.

1. The kava-pyrone kawain and dihydromethysticin are constituents of *Piper methysticum* which exert anticonvulsant, analgesic and anxiolytic properties. 2. In the present study the effect of these kava-pyrone were tested on field potential changes (fp) induced by omission of the extracellular  $Mg^{2+}$ , recorded from the area CA1 and CA3 of the hippocampal slice preparation of guinea pigs. These fp are generated by an activation of NMDA receptors and voltage dependent calcium channels. 3. Kawain and dihydromethysticin reduced reversibly the frequency of occurrence of fp in a concentration range from 5 to 40  $\mu\text{mol/l}$  and 10 to 40  $\mu\text{mol/l}$ , respectively. 4. Reduction of the fp frequency after addition of subthreshold concentrations of 5  $\mu\text{mol/l}$  kawain and 10  $\mu\text{mol/l}$  dihydromethysticin indicated additive actions of both drugs. 5. Since the serotonin-1A agonist ipsapirone also exerts anxiolytic effects, subthreshold concentrations of kawain or dihydromethysticin were combined with a subthreshold concentration of ipsapirone in another set of experiments. Combining kawain and ipsapirone or dihydromethysticin and ipsapirone caused a reduction of the rate of fp to 0.76 and 0.81 of the baseline value, respectively. 6. The findings suggest that (i) single constituents of *Piper methysticum* may have additive actions, (ii) that the two components kawain and dihydromethysticin may enhance the effects of the anxiolytic serotonin-1A agonist ipsapirone and (iii) that activation of NMDA receptors and/or voltage dependent calcium channels may be involved in the elementary mechanism of action of some kava-pyrone.