

Chemosensitization of carmustine with maitake beta-glucan on androgen-independent prostatic cancer cells: involvement of glyoxalase I.

Finkelstein MP, Aynehchi S, Samadi AA, et al. *J Altern Complement Med* 2002;8:573-580.

OBJECTIVE: To improve the poor efficacy (< 10%) of chemotherapy for patients with hormone-refractory prostate cancer, we investigated a possible cytotoxic effect of carmustine/beta-glucan combination on prostatic cancer PC-3 cells, focusing on a glutathione-dependent detoxifying enzyme, glyoxalase I (Gly-I). **METHODS:** Carmustine (BCNU) is an anticancer agent and a putative inhibitor of Gly-I, while beta-glucan is a unique, nontoxic polysaccharide extracted from maitake mushrooms. The cytotoxic effects of BCNU or other anticancer agents with beta-glucan on PC-3 cells were assessed by cell-viability testing and Gly-I activity was measured using the spectrophotometric method. **RESULTS:** BCNU, 5-fluorouracil (5-FU), and methotrexate (MTX) were capable of inducing approximately a 50% reduction in cell viability at 72 hours, while etoposide, cisplatin, and mitomycin C were all ineffective. Only the combination of BCNU (50 micro ;mol) and beta-glucan (60 micro g/mL) exhibited an enhanced cytotoxicity with an approximate 90% cell viability reduction, but little improvement was seen with any combinations of 5-FU, MTX, or beta-glucon. Gly-I assays revealed that such a profound (approximately 90%) cell death was accompanied by an approximate 80% reduction in Gly-I activity by 6 hours. **CONCLUSION:** This study demonstrates a sensitized cytotoxic effect of BCNU with beta-glucan in PC-3 cells, which was associated with a drastic (approximately 80%) inactivation of Gly-I. Therefore, the BCNU/beta-glucan combination may help to improve current treatment efficacy by targeting Gly-I, which appears to be critically involved in prostate cancer viability.

Possible ameliorative effect of taurine in the treatment of iron-deficiency anaemia in female university students of Gaza, Palestine.

Sirdah MM, El-Agouza IM, Abu Shahla AN. *Eur J Haematol* 2002;69:236-242.

The aim of the study was to evaluate the haematological effects of adding the antioxidant taurine to iron sulfate in the treatment of iron-deficiency anaemia (IDA). A sample of 730 students from Al-Azhar University, Gaza, in Palestine underwent screening with complete blood counts and serum samples. In subjects with microcytosis/hypochromasia, Alpha2 delta2 (HbA2) and serum concentrations of iron, total iron binding capacity (TIBC), ferritin and taurine were determined. Samples from 17 normocytic, normochromic, and non-anaemic subjects were used as baseline controls. At base-line, 81 of the 730 subjects (11.1%) had microcytosis/hypochromasia, 26 (3.6%) were diagnosed as beta-thalassemia carriers, none of which was iron deficient. Four subjects had microcytosis of unknown cause. Fifty-one subjects (all females) had iron-deficiency anaemia and were included in the therapeutic study, which lasted for 20 wk. They were matched for Hb into pairs and were treated with oral iron (325 mg of slow-release iron sulfate). In addition, they were, in a double-blind procedure, randomised to additional oral taurine (1000 mg d(-1)) at a cost comparable to that of adding ascorbic acid) or placebo. Mean S-aurine was significantly lower in the IDA subjects than in the controls. After 20 wk of iron supplementation, both the taurine and placebo group significantly improved their Hb concentrations and normalised the markers of iron deficiency. Apart from the expected, albeit in this study mild side-effects of oral iron, no significant side-effects were noted. In the taurine group, there was a statistically significant additive positive change from the baseline values on Hb (2.67 +/- 1.24 g dL(-1)), red blood cell (RBC) count [(0.57 +/- 0.25) x 10¹² L(-1)] and serum ferritin (30.33 +/- 17.99 microg L(-1)) as compared to placebo group

Protodioscin isolated from fenugreek (*Trigonella foenumgraecum* L.) induces cell death and morphological change indicative of apoptosis in leukemic cell line H-60, but not in gastric cancer cell line KATO III.

Hibasami H, Moteki H, Ishikawa K, et al. *Int J Mol Med* 2003;11:23-26.

Protodioscin (PD) was purified from fenugreek (*Trigonella foenumgraecum* L.) and identified by Mass, and ¹H- and ¹³C-NMR. The effects of PD on cell viability in human leukemia HL-60 and human stomach cancer KATO III cells were investigated. PD displayed strong growth inhibitory effect against HL-60 cells, but weak growth inhibitory effect on KATO III cells. Morphological change showing apoptotic bodies was observed in the HL-60 cells treated with PD, but not in KATO III cells treated with PD. Flow cytometric analysis showed that the hypodiploid nuclei of HL-60 cells were increased to 75.2, 96.3, and 100% after a 3-day treatment with 2.5, 5, and 10 micro M PD, respectively. The fragmentation by PD of DNA to oligonucleosomal-sized fragments, that is a characteristic of apoptosis, was observed to be both concentration- and time-dependent in the HL-60 cells. These findings suggest that growth inhibition by PD of HL-60 cells results from the induction of apoptosis by this compound in HL-60 cells.

Induction of apoptosis in low to moderate-grade human prostate carcinoma by red clover-derived dietary isoflavones.

Jarred RA, Keikha M, Dowling C, et al. *Cancer Epidemiol Biomarkers Prev* 2002;11:1689-1696.

Epidemiological evidence suggests a geographical basis for the incidence of prostate cancer and dietary factors, including isoflavone consumption, may be linked to this phenomenon. This paper reports a nonrandomized, nonblinded trial with historically matched controls from archival tissue designed to determine the effects of acute exposure to a dietary supplement of isoflavones in men with clinically significant prostate cancer before radical prostatectomy. Thirty-eight patients were recruited to the study upon diagnosis of prostate cancer. Before surgery, 20 men consumed 160 mg/day of red clover-derived dietary isoflavones, containing a mixture of genistein, daidzein, formononetin, and biochanin A. Serum PSA, testosterone, and biochemical factors were measured, and clinical and pathological parameters were recorded. The incidence of apoptosis in prostate tumor cells from radical prostatectomy specimens was compared between 18 treated and 18 untreated control tissues. There were no significant differences between pre- and posttreatment serum PSA, Gleason score, serum testosterone, or biochemical factors in the treated patients ($P > 0.05$). Apoptosis in radical prostatectomy specimens from treated patients was significantly higher than in control subjects ($P = 0.0018$), specifically in regions of low to moderate-grade cancer (Gleason grade 1-3). No adverse events related to the treatment were reported. This report suggests that dietary isoflavones may halt the progression of prostate cancer by inducing apoptosis in low to moderate-grade tumors, potentially contributing to the lower incidence of clinically significant disease in Asian men. The assessment of new prostatic therapies aimed at increasing apoptosis should control for intake of dietary isoflavones.

Efficacy and tolerability of oral and intramuscular S-adenosyl-L-methionine 1,4-butanedisulfonate (S-AMe) in the treatment of major depression: comparison with imipramine in 2 multicenter studies.

Delle Chiaie R, Pancheri P, Scapicchio P. *Am J Clin Nutr* 2002;76:S1172-S1176.

BACKGROUND: S-Adenosyl-L-methionine (S-AMe), a natural compound, is the most important methyl donor in the central nervous system. In several clinical trials, S-AMe showed antidepressant activity. **OBJECTIVE:** Two multicenter studies were conducted in patients with a diagnosis of major depressive episode [baseline score on the 21-item Hamilton Depression Rating Scale (HAM-D) ≥ 18] to confirm the efficacy and safety of S-AMe in the treatment of major depression. In the first study (MC3), 1600 mg S-AMe/d was given orally; whereas, in the second study (MC4), 400 mg S-AMe/d was given intramuscularly. In both studies, the effects of S-AMe were compared with those of 150 mg imipramine/d given orally in a double-blind design. **DESIGN:** In MC3, 143 patients received oral S-AMe and 138 patients received imipramine for 6 wk. In MC4, 147 patients received S-AMe intramuscularly and 148 patients received imipramine for 4 wk. In both studies the 2 main efficacy measures were the final HAM-D score and the percentage of responders to Clinical Global Impression at the endpoint. Secondary efficacy measures were the endpoint Montgomery-Asberg Depression Rating Scale scores and the percentage of responders, responders being those patients showing a decrease in HAM-D score of $\geq 50\%$ from baseline. **RESULTS:** In both studies, the results of S-AMe and imipramine treatment did not differ significantly for any efficacy measure. However, significantly fewer adverse events were observed in the patients treated with S-AMe. **CONCLUSIONS:** The antidepressive efficacy of 1600 mg S-AMe/d orally and 400 mg S-AMe/d intramuscularly is comparable with that of 150 mg imipramine/d orally, but S-AMe is significantly better tolerated.

The importance of the ratio of omega-6/omega-3 essential fatty acids.

Simopoulos AP. *Biomed Pharmacother* 2002;56:365-379.

Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of approximately 1 whereas in Western diets the ratio is 15/1-16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today's Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a low omega-6/omega-3 ratio) exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2-3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries, that are being exported to the rest of the world.

Eicosapentaenoic acid improves endothelial function in hypertriglyceridemic subjects despite increased lipid oxidizability.

Okumura T, Fujioka Y, Morimoto S, et al. *Am J Med Sci* 2002;324:247-253.

BACKGROUND: Epidemiologic investigations suggest that fish oil, which contains eicosapentaenoic acid (EPA), has favorable cardiovascular effects. Fish oil improves endothelial function in subjects with hypercholesterolemia or diabetes. However, controversy persists regarding relationships between primary hypertriglyceridemia and endothelial dysfunction. Moreover, lipoproteins are more susceptible to oxidation in vitro after incorporation of fish oil. **METHODS:** We determined the effects of EPA on serum lipids, susceptibility of low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL) to oxidation, and endothelial function in hypertriglyceridemic (HTG) subjects. In 8 men with untreated primary hypertriglyceridemia (plasma triglyceride between 150 and 500 mg/dL) and 7 control subjects (triglyceride below 150 mg/dL), forearm blood flow (FBF) responses were tested. In HTG subjects, this was repeated 3 months after initiation of EPA (1800 mg/day). Cu²⁺-induced oxidation of VLDL and LDL was determined by serial measurement of conjugated dienes. We used lag time, which corresponded to the period when the lipoproteins were resistant to oxidation, as a parameter of oxidizability. FBF responses to acetylcholine and sodium nitroprusside were determined by strain-gauge plethysmography. **RESULTS:** Plasma triglyceride in HTG subjects fell 31% with EPA supplementation. Before EPA, VLDL and LDL lag times in HTG subjects were shorter than in control subjects. EPA further reduced lag time for VLDL but not LDL. The FBF response to acetylcholine (but not to nitroprusside) was significantly less in HTG subjects before EPA than in control subjects. EPA normalized the FBF response to acetylcholine. **CONCLUSIONS:** EPA improves endothelial function in HTG subjects despite increasing in VLDL oxidizability.

Neuroprotective effects of the green tea components theanine and catechins.

Kakuda T. *Biol Pharm Bull* 2002;25:1513-1518.

The neuroprotective effects of theanine and catechins contained in green tea are discussed. Although the death of cultured rat cortical neurons was induced by the application of glutamic acid, this neuronal death was suppressed with exposure to theanine. The death of hippocampal CA1 pyramidal neurons caused by transient forebrain ischemia in the gerbil was inhibited with the ventricular preadministration of theanine. The neuronal death of the hippocampal CA3 region by kainate was also prevented by the administration of theanine. Theanine has a higher binding capacity for the AMPA/kainate receptors than for NMDA receptors, although the binding capacity in all cases is markedly less than that of glutamic acid. The results of the present study suggest that the mechanism of the neuroprotective effect of theanine is related not only to the glutamate receptor but also to other mechanisms such as the glutamate transporter, although further studies are needed. One of the onset mechanisms for arteriosclerosis, a major factor in ischemic cerebrovascular disease, is probably the oxidative alteration of low-density lipoprotein (LDL) by active oxygen species. The oxidative alterations of LDL were shown to be prevented by tea catechins. Scavenging of (·)O₂(-) was also exhibited by tea catechins. The neuroprotective effects of theanine and catechins contained in green tea are a focus of considerable attention, and further studies are warranted.

Effects of lycopene supplementation in patients with localized prostate cancer.

Kucuk O, Sarkar FH, Djuric Z, et al. *Exp Biol Med* 2002;227:881-885.

Epidemiological studies have shown an inverse association between dietary intake of lycopene and prostate cancer risk. We conducted a clinical trial to investigate the biological and clinical effects of lycopene supplementation in patients with localized prostate cancer. Twenty-six men with newly diagnosed prostate cancer were randomly assigned to receive a tomato oleoresin extract containing 30 mg of lycopene (n = 15) or no supplementation (n = 11) for 3 weeks before radical prostatectomy. Biomarkers of cell proliferation and apoptosis were assessed by Western blot analysis in benign and cancerous prostate tissues. Oxidative stress was assessed by measuring the peripheral blood lymphocyte DNA oxidation product 5-hydroxymethyldeoxyuridine (5-OH-mdU). Usual dietary intake of nutrients was assessed by a food frequency questionnaire at baseline. Prostatectomy specimens were evaluated for pathologic stage, Gleason score, volume of cancer, and extent of high-grade prostatic intraepithelial neoplasia. Plasma levels of lycopene, insulin-like growth factor-1, insulin-like growth factor binding protein-3, and prostate-specific antigen were measured at baseline and after 3 weeks of supplementation or observation. After intervention, subjects in the intervention group had smaller tumors (80% vs 45%, less than 4 ml), less involvement of surgical margins and/or extra-prostatic tissues with cancer (73% vs 18%, organ-confined disease), and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia (33% vs 0%, focal involvement) compared with subjects in the control group. Mean plasma prostate-specific antigen levels were lower in the intervention group compared with the control group. This pilot study suggests that lycopene may have beneficial effects in prostate cancer. Larger clinical trials are warranted to investigate the potential preventive and/or therapeutic role of lycopene in prostate cancer.

Vitamin C and vitamin E supplement use and bladder cancer mortality in a large cohort of US men and women.

Jacobs EJ, Henion AK, Briggs PJ, et al. *Am J Epidemiol* 2002;156:1002-1010.

Some epidemiologic studies suggest that use of vitamin C or vitamin E supplements, both potent antioxidants, may reduce the risk of bladder cancer. The authors examined the association between use of individual vitamin C and vitamin E supplements and bladder cancer mortality among 991,522 US adults in the Cancer Prevention Study II (CPS-II) cohort. CPS-II participants completed a self-administered questionnaire at enrollment in 1982 and were followed regarding mortality through 1998. During follow-up, 1,289 bladder cancer deaths occurred (962 in men and 327 in women). Rate ratios were adjusted for age, sex, cigarette smoking, education, and consumption of citrus fruits and vegetables. Regular vitamin C supplement use (≥ 15 times per month) was not associated with bladder cancer mortality, regardless of duration (rate ratio (RR) = 0.91, 95% confidence interval (CI): 0.68, 1.20 for < 10 years' use; RR = 1.25, 95% CI: 0.91, 1.72 for ≥ 10 years' use). Regular vitamin E supplement use for ≥ 10 years was associated with a reduced risk of bladder cancer mortality (RR = 0.60, 95% CI: 0.37, 0.96), but regular use of shorter duration was not (RR = 1.04, 95% CI: 0.77, 1.40). Results support the hypothesis that long-duration vitamin E supplement use may reduce the risk of bladder cancer mortality.

Pseudodementia associated with use of ibuprofen.

Bernstein AL, Werlin A. *Ann Pharmacother* 2003;37:80-82.

OBJECTIVE: To report a case of dementing syndrome resulting from ibuprofen use. **CASE SUMMARY:** A 76-year-old white man with normal mental status became confused, was lost in familiar places, and showed short-term memory loss after beginning a therapeutic regimen of ibuprofen 600 mg 3 times daily for osteoarthritis in anticipation of embarking on a foreign trip. Symptoms of dementia began within 1 week after taking ibuprofen and resolved completely within 1 week after the ibuprofen regimen was stopped. This pattern was repeated 6 months later, when the patient again traveled abroad. Consistently before, during, and after these events, the patient took atenolol, clonidine, lisinopril, aspirin, vitamin C, lecithin, vitamin E, and multivitamins. **DISCUSSION:** Using the Naranjo probability scale, we reasoned that the patient's dementia-like syndrome could be attributed to the use of ibuprofen because pseudodementia appeared after the suspected drug was administered, improved when the drug was discontinued, reappeared when the drug was readministered, had no apparent alternative cause, manifested similarly after each exposure to ibuprofen, and was confirmed by the family's observation after both episodes. Objective causality assessment revealed that the adverse drug reaction was probable. **CONCLUSIONS:** Use of ibuprofen must be considered during clinical evaluation of any patient with new onset of dementing illness. The Naranjo probability scale may be clinically useful for evaluating other pharmaceutical agents that may be contributing to development of dementia-like conditions.

Ascorbic acid reduces blood pressure and arterial stiffness in type 2 diabetes.

Mullan BA, Young IS, Fee H, McCance DR. *Hypertension* 2002;40:804-809.

Experimental evidence suggests that acute parenteral administration of high-dose ascorbic acid has beneficial vascular effects in type 2 diabetes. We studied the hemodynamic effects of chronic oral supplementation in this condition. Thirty patients, 45 to 70 years of age, with type 2 diabetes, were randomly assigned in a double-blind manner to receive 500 mg ascorbic acid daily by mouth or placebo. Patients were studied at baseline and after 4 weeks of assigned treatment. The central aortic augmentation index (AgIx) and the time to wave reflection (Tr) were derived from radial artery pulse wave analysis data. AgIx and Tr were used as measures of systemic arterial stiffness and aortic stiffness, respectively. Ascorbic acid decreased brachial systolic blood pressure from 142.1±12.6 (SD) to 132.3±12.1 mm Hg (difference [95% CI] 9.9 [4.7, 15.0]; P<0.01), brachial diastolic pressure from 83.9±4.8 to 79.5±6.0 mm Hg (4.4 [1.8, 7.0]; P<0.01), and AgIx from 26.8±5.5% to 22.5±6.8% (4.3 [1.5, 7.1]; P<0.01). Tr increased from 137.1±12.6 to 143.4±9.2 ms (-6.3 [-10.1, -2.5]; P<0.01). Placebo had no hemodynamic effects, and this difference between treatments was significant (P<0.01 for blood pressure and Tr, P=0.03 for AgIx). We have therefore shown that after 1 month, oral ascorbic acid lowered arterial blood pressure and improved arterial stiffness in patients with type 2 diabetes. As strict control of blood pressure reduces cardiovascular risk in diabetes, ascorbic acid supplementation may potentially be a useful and inexpensive adjunctive therapy. Larger and longer studies now need to be performed.

L-Arginine and L-Lysine stimulation on cultured human osteoblasts.

Torricelli P, Fini M, Giavaresi G, et al. *Biomed Pharmacother* 2002;56:492-497.

Essential amino acids, such as L-Arginine (Arg) and L-Lysine (Lys), are involved in bone metabolism and growth. Our previous studies analyzed the effect of these amino acids on rat osteoblast cultures and in experimental animals. In this study, we evaluated the effect of L-Arg and L-Lys on cultured human osteoblasts. Primary human osteoblast cultures were divided into four groups: the Arg Group received 0.625 mg/ml per day of Arg, the Lys Group 0.587 mg/ml per day of Lys, the Arg-Lys Group received both amino acids, whereas the Control Group was sham-treated. After 7 days, the following parameters were tested in all groups: alkaline phosphatase (ALP), nitric oxide (NO), calcium (Ca), phosphorus (P), osteocalcin (OC), type I collagen (PICP), interleukin-6 (IL-6), transforming growth factor-beta 1 (TGF-beta 1) on culture supernatant, platelet derived growth factor (PDGF), insulin-like growth factor-I (IGF-I), and MTT proliferation test on cells. Arg administration significantly increased ALP, NO, PICP and IGF-I production and reduced the level of IL-6. Lys administration over the same time interval mainly affected cell proliferation, as evidenced by the MTT test and immunostaining for PDGF. The same positive effects evidenced by the single administrations of the two amino acids resulted from their simultaneous administration. However, synergism could be demonstrated only for the decrease in the level of IL-6. Arg and Lys show a positive effect on human osteoblasts, which is related partly to the production of those factors required for matrix synthesis, and partly to the direct or mediated activation of cell proliferation.

Two years of treatment with recombinant human growth hormone increases bone mineral density in men with idiopathic osteoporosis.

Gillberg P, Mallmin H, Petren-Mallmin M, et al. *J Clin Endocrinol Metab* 2002;87:4900-4906.

We have investigated the effects of GH treatment on bone turnover, bone size, bone mineral density (BMD), and bone mineral content (BMC) in 29 men, 27-62 yr old, with idiopathic osteoporosis. The patients were randomly assigned to treatment with GH, either as continuous treatment with daily injections of 0.4 mg GH/d (group A, n = 14) or as intermittent treatment with 0.8 mg GH/d for 14 d every 3 months (group B, n = 15). All patients were treated with GH for 24 months, with a follow-up period of 12 months, and also received 500 mg calcium and 400 U vitamin D3 daily during all 36 months. Fasting morning urine and serum samples were obtained for assay of IGF-I, bone markers, and routine laboratory tests at baseline, after 1, 12, 24, and 36 months. Body composition, BMD, and BMC were determined by dual-energy x-ray absorptiometry at baseline and every 6 months. After 2 yr, there was an increase in BMD in lumbar spine (by 4.1%) in group A, and in total body (by 2.6%) in group A and (by 2.7%) in group B. BMC of the total body and lean body mass increased, whereas fat mass decreased in both treatment groups. After 36 months, the BMD and BMC in lumbar spine and total body had increased further in both groups. We conclude that 2 yr of intermittent or continuous treatment with GH in men with idiopathic osteoporosis results in an increase in BMD and BMC that is sustained for at least 1 yr post treatment.

Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial.

Waters DD, Alderman EL, Hsia J, et al. *JAMA* 2002;288:2432-2440.

CONTEXT: Hormone replacement therapy (HRT) and antioxidant vitamins are widely used for secondary prevention in postmenopausal women with coronary disease, but no clinical trials have demonstrated benefit to support their use. **OBJECTIVE:** To determine whether HRT or antioxidant vitamin supplements, alone or in combination, influence the progression of coronary artery disease in postmenopausal women, as measured by serial quantitative coronary angiography. **DESIGN, SETTING, AND PATIENTS:** The Women's Angiographic Vitamin and Estrogen (WAVE) Trial, a randomized, double-blind trial of 423 postmenopausal women with at least one 15% to 75% coronary stenosis at baseline coronary angiography. The trial was conducted from July 1997 to January 2002 in 7 clinical centers in the United States and Canada. **INTERVENTIONS:** Patients were randomly assigned in a 2 x 2 factorial design to receive either 0.625 mg/d of conjugated equine estrogen (plus 2.5 mg/d of medroxyprogesterone acetate for women who had not had a hysterectomy), or matching placebo, and 400 IU of vitamin E twice daily plus 500 mg of vitamin C twice daily, or placebo. **MAIN OUTCOME MEASURE:** Annualized mean (SD) change in minimum lumen diameter (MLD) from baseline to concluding angiogram of all qualifying coronary lesions averaged for each patient. Patients with intercurrent death or myocardial infarction (MI) were imputed the worst rank of angiographic outcome. **RESULTS:** The mean (SD) interval between angiograms was 2.8 (0.9) years. Coronary progression, measured in mean (SD) change, worsened with HRT by 0.047 (0.15) mm/y and by 0.024 (0.15) mm/y with HRT placebo ($P = .17$); and for antioxidant vitamins by 0.044 (0.15) mm/y and with vitamin placebo by 0.028 (0.15) mm/y ($P = .32$). When patients with intercurrent death or MI were included, the primary outcome showed an increased

risk for women in the active HRT group ($P = .045$), and suggested an increased risk in the active vitamin group ($P = .09$). Fourteen patients died in the HRT group and 8 in the HRT placebo group (hazard ratio [HR], 1.8; 95% confidence interval [CI], 0.75-4.3), and 16 in the vitamin group and 6 in the vitamin placebo group (HR, 2.8; 95% CI, 1.1-7.2). Death, nonfatal MI, or stroke occurred in 26 HRT patients vs 15 HRT controls (HR, 1.9; 95% CI, 0.97-3.6) and in 26 vitamin patients and 18 vitamin controls (HR, 1.5; 95% CI, 0.80-2.9). There was no interaction between the 2 treatment interventions. **CONCLUSION:** In postmenopausal women with coronary disease, neither HRT nor antioxidant vitamin supplements provide cardiovascular benefit. Instead, a potential for harm was suggested with each treatment.

Preventing kidney stones: calcium restriction not warranted.

Hall PM. *Cleve Clin J Med* 2002;69:885-888.

The traditional wisdom on preventing calcium stones, the most common form of kidney stone, has been to advise patients to limit dietary calcium. Research has proved this wrong, however. Normal dietary calcium intake, along with reduced salt and protein, is now advised. This paper also summarizes the diagnosis and treatment of the less-common forms of kidney stones-struvite, uric acid, and cystine.

Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study.

Zandi PP, Carlson MC, Plassman BL, et al. *JAMA* 2002;288:2123-2129.

CONTEXT: Previous studies have shown a sex-specific increased risk of Alzheimer disease (AD) in women older than 80 years. Basic neuroscience findings suggest that hormone replacement therapy (HRT) could reduce a woman's risk of AD. Epidemiologic findings on AD and HRT are mixed. **OBJECTIVE:** To examine the relationship between use of HRT and risk of AD among elderly women. **DESIGN, SETTING, AND PARTICIPANTS:** Prospective study of incident dementia among 1357 men (mean age, 73.2 years) and 1889 women (mean age, 74.5 years) residing in a single county in Utah. Participants were first assessed in 1995-1997, with follow-up conducted in 1998-2000. History of women's current and former use of HRT, as well as of calcium and multivitamin supplements, was ascertained at the initial contact. **MAIN OUTCOME MEASURE:** Diagnosis of incident AD. **RESULTS:** Thirty-five men (2.6%) and 88 women (4.7%) developed AD between the initial interview and time of the follow-up (3 years). Incidence among women increased after age 80 years and exceeded the risk among men of similar age (adjusted hazard ratio [HR], 2.11; 95% confidence interval [CI], 1.22-3.86). Women who used HRT had a reduced risk of AD (26 cases among 1066 women) compared with non-HRT users (58 cases among 800 women) (adjusted HR, 0.59; 95% CI, 0.36-0.96). Risk varied with duration of HRT use, so that a woman's sex-specific increase in risk disappeared entirely with more than 10 years of treatment (7 cases among 427 women). Adjusted HRs were 0.41 (95% CI, 0.17-0.86) for HRT users compared with nonusers and 0.77 (95% CI, 0.31-1.67) compared with men. No similar effect was seen with calcium or multivitamin use. Almost all of the HRT-related reduction in incidence reflected former use of HRT (9 cases among 490 women; adjusted HR, 0.33 [95% CI, 0.15-0.65]). There was no effect with current HRT use (17 cases among 576 women; adjusted HR, 1.08 [95% CI, 0.59-1.91]) unless duration of treatment exceeded 10 years (6 cases among 344 women;

adjusted HR, 0.55 [95% CI, 0.21-1.23]). **CONCLUSIONS:** Prior HRT use is associated with reduced risk of AD, but there is no apparent benefit with current HRT use unless such use has exceeded 10 years.

Diet and Parkinson's disease: a potential role of dairy products in men.

Chen H, Zhang SM, Hernan MA, et al. *Ann Neurol* 2002;52:793-801.

Diet may play a causative role in Parkinson's disease (PD), but potential associations between diet and PD risk rarely have been assessed in prospective studies. We investigated associations between food intakes and PD risk in two large prospective cohorts in which 210 incident PD cases in men and 184 in women were documented. A positive association was found between dairy intake and PD risk in men (relative risk [RR] comparing extreme categories, 1.8; p trend = 0.004), but not in women (RR, 1.1; p trend = 0.9). No other food groups were associated with PD risk in either men or women. Further analyses among men showed significant positive associations with PD risk for intakes of several dairy foods as well as dairy calcium (RR, 1.5; p trend = 0.02), dairy vitamin D (RR, 1.6; p trend = 0.004), dairy protein (RR, 1.6; p trend = 0.01), and lactose (RR, 1.8; p trend = 0.002), but not dairy fat (RR, 1.1; p trend = 0.4). Intakes of calcium, vitamin D, and protein from other dietary or supplemental sources were not related to PD risk in men. Our results suggest that higher intake of dairy products may increase the risk of PD in men; however, this finding needs further evaluation, and the underlying active components need to be identified.

C-reactive protein relaxes human vessels in vitro.

Sternik L, Samee S, Schaff HV, et al. *Arterioscler Thromb Vasc Biol* 2002;22:1865-1868.

OBJECTIVE: C-reactive protein (CRP) is a sensitive marker of inflammation and a prognostic marker in cardiovascular disease. Evidence suggests direct biological activities of CRP within the vascular wall. The study was designed to examine the vasoreactive effects of CRP. **METHODS AND RESULTS:** Human internal mammary artery rings were obtained during cardiovascular bypass surgery and suspended in an organ bath chamber. The rings were precontracted with endothelin-1, and response to cumulative concentrations of CRP was obtained. Experiments were repeated after initial incubation with 20, 40, and 60 mmol/L KCl, the potassium channel blockers BaCl, tetraethylammonium chloride, and glibenclamide, and the NO synthase inhibitor N-monomethyl-L-arginine and also after removal of the endothelium. CRP caused dose-dependent relaxation of human internal mammary artery rings, which was not affected by preincubation with N-monomethyl-L-arginine or removal of the endothelium. Maximum relaxation response to CRP (79.5±10%) was attenuated by KCl (2.5±11.5%, P<0.001), BaCl (24.5±7.5%, P<0.001), and tetraethylammonium chloride (34.9±8.25%, P<0.01) but not by glibenclamide. **Conclusions-** The present study demonstrates that CRP exerts an endothelium-independent vasorelaxing effect via potassium channels. Thus, the study suggests a role of CRP in the regulation of vascular tone.

Food allergies in children affect nutrient intake and growth.

Christie L, Hine RJ, Parker JG, Burks W. *J Am Diet Assoc* 2002;102:1648-1651.

OBJECTIVES: To identify if specific food allergies, elimination diets, or other variables associated with food allergies have an impact on the growth and nutrient intake of children with food allergies. **DESIGN:** Measurements of height, weight, and body mass index were used to determine potential growth problems. Estimates of energy and nutrient intakes were based on 3-day diet records. A questionnaire was used to determine number of food allergies and other variables. **SUBJECTS:** Ninety-eight children with food allergies (subjects, mean age 3.7 ± 2.3 years) and 99 children without food allergies (controls, mean age 4.1 ± 2.4 years) participated in this age-matched, consecutive sampling, cross-sectional study. **STATISTICAL ANALYSIS PERFORMED:** Cochran-Mantel-Haenszel statistics using general association and Fisher Exact Test, with 2-sided probability, were conducted. **RESULTS:** Children with two or more food allergies were shorter, based on height-for-age percentiles, than those with one food allergy (P<.05). More than 25% of children in both groups consumed less than 67% of the DRI (RDA or AI) for calcium, vitamin D, and vitamin E. More children with cow's milk allergy or multiple food allergies consumed dietary calcium less than age- and gender-specific recommendations compared with children without cow's milk allergy and/or one food allergy. The possibility of consuming a less than recommended intake of calcium and vitamin D in children with food allergy was less if the child received nutrition counseling (P<.05) or consumed a safe infant/toddler formula or fortified soy beverage. **APPLICATIONS/CONCLUSIONS:** Children diagnosed with food allergies need an annual nutrition assessment to prevent growth problems or inadequate nutrient intake. Children with milk allergies or multiple food allergies are at greater risk. Nutrition education needs to address how to avoid all forms of the allergen and incorporate alternative nutrient-dense foods. This population would benefit from the development and validation of a medical nutrition therapy protocol.

Preliminary comparison of bromelain and ibuprofen for delayed onset muscle soreness management.

Stone MB, Merrick MA, Ingersoll CD, Edwards JE. *Clin J Sport Med* 2002;12:373-378.

OBJECTIVE The purpose of this study was to determine whether a common bromelain regimen or common ibuprofen regimen are effective in resolving pain and muscle dysfunction associated with delayed onset muscle soreness of the elbow flexors. **DESIGN** A randomized, double-blinded, repeated measures design was used for this study. **SETTING** The study was performed in the Sports Injury Research Lab at an NCAA Division I university. **PARTICIPANTS** Forty subjects who had not participated in an upper body resistance-training program 3 months prior to the study, suffered pain or injury in the nondominant arm, or experienced an adverse response to nonsteroidal anti-inflammatory drugs or pineapple (bromelain source) were recruited. Thirty-nine subjects finished the study. **INTERVENTIONS** Active range of motion (ROM), perceived pain, and peak concentric torque measurements of the nondominant arm were taken prior to and 24, 48, 72, and 96 hours following an eccentric exercise protocol of the elbow flexors. Subjects were assigned to one of four treatment groups (bromelain 300 mg t.i.d., ibuprofen 400 mg t.i.d., placebo t.i.d., and control) and began treatment immediately following the exercise protocol. **MAIN OUTCOME MEASURES** No differences among treatments were observed for any of the dependent variables at any time. ROM deficits and pain peaked between 48 and 72 hours. Peak torque deficiencies were observed between 24 and 72 hours. **CONCLUSIONS** Ingestion of bromelain and ibuprofen had no effect on elbow flexor pain, loss of ROM, or loss of concentric peak torque as a result of an eccentric exercise regimen.

Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients.

Nathens AB, Neff MJ, Jurkovich GJ, et al. *Ann Surg* 2002;236:814-822.

OBJECTIVE To determine the effectiveness of early, routine antioxidant supplementation using alpha-tocopherol and ascorbic acid in reducing the rate of pulmonary morbidity and organ dysfunction in critically ill surgical patients. **SUMMARY BACKGROUND DATA** Oxidative stress has been associated with the development of the acute respiratory distress syndrome (ARDS) and organ failure through direct tissue injury and activation of genes integral to the inflammatory response. In addition, depletion of endogenous antioxidants has been associated with an increased risk of nosocomial infections. The authors postulated that antioxidant supplementation in critically ill surgical patients may reduce the incidence of ARDS, pneumonia, and organ dysfunction. **METHODS** This randomized, prospective study was conducted to compare outcomes in patients receiving antioxidant supplementation (alpha-tocopherol and ascorbate) versus those receiving standard care. The primary endpoint for analysis was pulmonary morbidity (a composite measure of ARDS and nosocomial pneumonia). Secondary endpoints included the development of multiple organ failure, duration of mechanical ventilation, length of ICU stay, and mortality. **RESULTS** Five hundred ninety-five patients were enrolled and analyzed, 91% of whom were victims of trauma. The relative risk of pulmonary morbidity was 0.81 (95% confidence interval 0.60-1.1) in patients receiving antioxidant supplementation. Multiple organ failure was significantly less likely to occur in patients receiving antioxidants than in patients receiving standard care, with a relative risk of 0.43 (95% confidence interval 0.19-0.96). Patients randomized to antioxidant supplementation also had a shorter duration of mechanical ventilation and length of ICU stay. **CONCLUSIONS** The early administration of antioxidant supplementation using alpha-tocopherol and ascorbic acid reduces the incidence of organ failure and shortens ICU length of stay in this cohort of critically ill surgical patients.

Effect of discontinuation of estrogen, calcitriol, and the combination of both on bone density and bone markers.

Gallagher JC, Rapuri PB, Haynatzki G, Detter JR. *J Clin Endocrinol Metab* 2002;87:4914-4923.

In a 5-yr randomized prospective study we examined the treatment effect of estrogen replacement therapy/hormone replacement therapy (ERT/HRT), calcitriol, ERT/HRT and calcitriol, or placebo for 3 yr and the effect of discontinuation of therapy for 2 more yr on bone mineral density (BMD), calciotropic hormones, markers of bone remodeling, and calcium absorption in 489 elderly women. The treatment phase of the study was double-blinded. After discontinuing therapy for 2 yr, there was rapid bone loss in all 3 treatment groups, and most of the decrease in BMD occurred in the first year. In the ERT/HRT group, spine BMD increased 5.5% in yr 3, decreased 3.2% in yr 4, and decreased 0.7% in yr 5; femoral neck BMD increased 3.7% in yr 3, decreased 2.5% in yr 4, and decreased 0.4% in yr 5; total body BMD increased 2.1% in yr 3, decreased 1.4% in yr 4, and decreased 0.6% in yr 5. In the combination group, spine BMD increased 7.1% in yr 3, decreased 4.3% in yr 4, and decreased 0.3% in yr 5; femoral neck BMD increased 4.5% in yr 3, decreased 3.0% in yr 4, and decreased 0.01% in yr 5; total body BMD increased 2.2% in yr 3, decreased 1.5% in yr 4, and decreased 0.6% in yr 5. In the calcitriol group, spine BMD increased 1.8% in yr 3, decreased 1.8% in yr 4, and showed no change in yr 5; femoral neck BMD increased 0.2% in yr 3, decreased 0.2% in yr 4, and decreased 0.6% in yr 5; total body BMD decreased 0.4% in yr 3, decreased 0.6% in yr 4, and decreased 0.4% in yr 5. Compared with placebo, all treated groups at yr 5 had significantly higher total body BMD; only the combination group had significantly higher spine BMD (3.4%; $P < 0.001$) and total hip BMD (2.4%; $P < 0.01$.) compared with the placebo group. Compared with baseline, only spine BMD in the combination group was significantly higher (2.6%; $P < 0.001$) at yr 5. The increase in calcium absorption and the decrease in serum PTH levels in the calcitriol groups were reversed after discontinuation of treatment, and the decrease in bone markers

was reversed in the hormone-treated groups. These results suggest that discontinuation of ERT/HRT and/or calcitriol therapy in elderly women leads to a decrease in much of the BMD gained on treatment; however, in the combination group there was a statistically significant residual effect on spine BMD.

Hepatic toxicity possibly associated with kava-containing products – United States, Germany, and Switzerland, 1999-2002.

MMWR Morb Mortal Wkly Rep 2002;51:1065-1067.

Since 1999, health-care professionals in Germany, Switzerland, and the United States have reported the occurrence of severe hepatic toxicity possibly associated with the consumption of products containing kava (i.e., kava kava or Piper methysticum). A total of 11 patients who used kava products had liver failure and underwent subsequent liver transplantation. On March 25, 2002, in response to five such case reports (four in Europe and one in the United States), the Food and Drug Administration (FDA) issued a consumer advisory and subsequently completed an investigation already underway of a similar U.S. case. This report presents the investigation of the two U.S. cases of liver failure associated with kava-containing dietary supplement products and summarizes the European cases. FDA continues to advise consumers and health-care providers about the potential risk associated with the use of kava-containing products.

Silibinin strongly synergizes human prostate carcinoma DU145 cells to doxorubicin-induced growth inhibition, G2-M arrest, and apoptosis.

Tyagi AK, Singh RP, Agarwal C, et al.
Clin Cancer Res 2002;8:3512-3519.

PURPOSE: We recently demonstrated the strong anticancer efficacy of silibinin, an active constituent of a widely consumed dietary supplement milk thistle extract, against human prostate cancer cells in culture and nude mice xenografts. We also observed that pharmacologically achievable concentrations of silibinin in animal studies were in the range of 25-100 microM, depending on the dose regimen, which did not show any apparent toxicity to the animals. In this study, we assessed whether silibinin synergizes the therapeutic potential of the chemotherapeutic drug doxorubicin against prostate cancer, the effectiveness of which is limited because of high systemic toxicity. **EXPERIMENTAL DESIGN:** Prostate cancer cells were treated with silibinin and doxorubicin, either alone or in combination, and cell growth was determined by manual cell counting. Cell cycle progression was assessed by saponin/propidium iodide staining and fluorescence-activated cell sorter analysis. Protein levels of cell cycle regulators were determined by Western blotting, and cdc2/p34 kinase activity was analyzed by in-beads kinase assay. Apoptosis was quantified by annexin V/propidium iodide staining and fluorescence-activated cell sorter analysis. **RESULTS:** Silibinin strongly synergized the growth-inhibitory effect of doxorubicin in prostate carcinoma DU145 cells (combination index, 0.235-0.587), which was associated with a strong G(2)-M arrest in cell cycle progression, showing 88% cells in G2-M phase by this combination compared with 19 and 41% of cells in silibinin and doxorubicin treatment alone, respectively. The underlying mechanism of G2-M arrest showed a strong inhibitory effect of combination on cdc25C, cdc2/p34, and cyclin B1 protein expression and cdc2/p34 kinase activity. More importantly, this combination caused 41% apoptotic cell death compared with 15% by either agent alone. Silibinin and doxorubicin alone as well as in combination were also effective in inhibiting the growth of

androgen-dependent prostate carcinoma LNCaP cells. **CONCLUSION:** These findings suggest a need for in vivo studies with this combination in preclinical prostate cancer models. Positive outcomes might be relevant for a clinical application in prostate cancer patients.

Coenzyme Q-responsive Leigh's encephalopathy in two sisters.

Van Maldergem L, Trijbels F, DiMauro S, et al.
Ann Neurol 2002;52:750-754.

A 31-year-old woman had encephalopathy, growth retardation, infantilism, ataxia, deafness, lactic acidosis, and increased signals of caudate and putamen on brain magnetic resonance imaging. Muscle biochemistry showed succinate:cytochrome c oxidoreductase (complex II-III) deficiency. Both clinical and biochemical abnormalities improved remarkably with coenzyme Q10 supplementation. Clinically, when taking 300mg coenzyme Q10 per day, she resumed walking, gained weight, underwent puberty, and grew 20cm between 24 and 29 years of age. Coenzyme Q10 was markedly decreased in cerebrospinal fluid, muscle, lymphoblasts, and fibroblasts, suggesting the diagnosis of primary coenzyme Q10 deficiency. An older sister has similar clinical course and biochemical abnormalities. These findings suggest that coenzyme Q10 deficiency can present as adult Leigh's syndrome.

Melatonin metabolite excretion among cellular telephone users.

Burch JB, Reif JS, Noonan CW, et al.
Int J Radiat Biol 2002;78:1029-1036.

PURPOSE: The relationship between cellular telephone use and excretion of the melatonin metabolite 6-hydroxymelatonin sulfate (6-OHMS) was evaluated in two populations of male electric utility workers (Study 1, n=149; Study 2, n=77). **MATERIALS AND METHODS:** Participants collected urine samples and recorded cellular telephone use over 3 consecutive workdays. Personal 60-Hz magnetic field (MF) and ambient light exposures were characterized on the same days using EMDEX II meters. A repeated measures analysis was used to assess the effects of cellular telephone use, alone and combined with MF exposures, after adjustment for age, participation month and light exposure. **RESULTS:** No change in 6-OHMS excretion was observed among those with daily cellular telephone use >25 min in Study 1 (5 worker-days). Study 2 workers with >25 min cellular telephone use per day (13 worker-days) had lower creatinine-adjusted mean nocturnal 6-OHMS concentrations (p=0.05) and overnight 6-OHMS excretion (p=0.03) compared with those without cellular telephone use. There was also a linear trend of decreasing mean nocturnal 6-OHMS/creatinine concentrations (p=0.02) and overnight 6-OHMS excretion (p=0.08) across categories of increasing cellular telephone use. A combined effect of cellular telephone use and occupational 60-Hz MF exposure in reducing 6-OHMS excretion was also observed in Study 2. **CONCLUSIONS:** Exposure-related reductions in 6-OHMS excretion were observed in Study 2, where daily cellular telephone use of >25 min was more prevalent. Prolonged use of cellular telephones may lead to reduced melatonin production, and elevated 60-Hz MF exposures may potentiate the effect.

The metabolic response to intravenous medium-chain triglycerides in infants after surgery.

Donnell SC, Lloyd DA, Eaton S, Pierro A. *J Pediatr* 2002;141:689-694.

OBJECTIVE: The aim of this study was to determine if administration of mixed medium-chain triglycerides (MCT)/long chain triglycerides (LCT) fat emulsion would increase net fat oxidation and if carbohydrate intake would influence net fat oxidation. **STUDY DESIGN:** Stable infants receiving total parenteral nutrition were studied after surgery. Respiratory gas exchange was measured by indirect calorimetry and urinary nitrogen excretion by the micro-Kjeldahl method. Intravenous fat (4 g/kg/day) was given as either pure LCT fat emulsion or 50/50 MCT/LCT fat emulsion. Carbohydrate intake was either "high" (15 g/kg/day) or "low" (10 g/kg/day). Four groups of patients were studied: group 1 = LCT and high-carbohydrate; group 2 = LCT and low-carbohydrate; group 3 = MCT/LCT and high-carbohydrate; group 4 = MCT/LCT and low-carbohydrate. **RESULTS:** At a carbohydrate intake of 15 g/kg/day, the calories available from glucose exceeded the measured resting energy expenditure (REE), and no differences were seen in either energy expenditure or net fat oxidation between patients receiving LCT and MCT/LCT fat emulsions. However, at a carbohydrate intake of 10 g/kg/day, when glucose calories were less than REE, net fat oxidation was significantly higher in patients receiving MCT/LCT (median, 1.94; range, 1.05-2.24 g/kg/day) compared with patients receiving LCT (median, 0.60; range, -0.09 to 1.35; P=.03). **CONCLUSION:** Providing that carbohydrate calories do not exceed REE, partial replacement of LCT by MCT in intravenous fat emulsions can increase net fat oxidation in infants after surgery.

Effects of low-dose omega-3 fatty acid substitution in type-2 diabetes mellitus with special reference to oxidative stress – a prospective preliminary study.

Jain S, Gaiha M, Bhattacharjee J, Anuradha S. *J Assoc Physicians India* 2002;50:1028-1033.

BACKGROUND: A state of increased oxidative stress has been recognised in type 2 diabetes mellitus (DM). The present study was done to assess the effects of low dose omega-3 fatty acids substitution in patients with type 2 DM with special reference to oxidative stress. **METHOD:** Sixty-five patients with type 2 DM of body mass index (BMI) < 27 kg/m² and thirty age and sex matched healthy controls were evaluated for blood glucose, blood pressure and lipid profile and oxidative stress was assessed in them by measuring lipid peroxides (LP), diene conjugates (DC) and reduced glutathione (RG) in the serum. Of the 65, 40 motivated patients were randomly divided into two groups—group 1 comprising of fifteen patients prescribed a diabetic diet along with a placebo and group 2 consisting of twenty-five patients on the same diet with the addition of 0.6 g omega-3 fatty acids as one capsule Maxigard (containing 180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid) twice daily. All parameters were reassessed after six weeks. **RESULTS:** The levels of lipid peroxides (micromol/L), diene conjugates (OD units) and reduced glutathione (mmol GSH/L) were significantly altered indicating increased oxidative stress in the diabetics compared to the healthy controls: 4.106 +/- 0.889, 2.751 +/- 0.424, 1.344 +/- 0.316 and 1.91 +/- 0.541, 1.735 +/- 0.315, 1.919 +/- 0.310, respectively (p < 0.001 for all the three). Patients in group 1 and 2 were comparable in all respects including oxidative stress at the start of therapy. After six weeks, on comparing the mean % changes in the three parameters of oxidative stress between the two groups, it was seen that the % change was significantly higher in group 2 (Maxigard group) compared to group 1 (Placebo): 5.22 +/- 1.056 (p = 0.05), 3.28 +/- 0.608 (p = 0.01), 5.27 +/- 0.585 (p < 0.001) and 0.82 +/- 0.123, 0.18 +/- 0.017, 0.56 +/- 0.035 (p < 0.001), respectively. The patients in group 2 also exhibited significantly

greater improvement in glycemic status, blood pressure and lipid profiles. **CONCLUSIONS:** The present study documented the existence of a state of increased oxidative stress in type 2 diabetics. Significant beneficial effects of low dose omega-3 fatty acids substitution for PUFA-6 were observed not only on oxidative stress parameters but also on blood pressure and metabolic profile.

Therapeutic potential of curcumin in human prostate cancer-I. Curcumin induces apoptosis in both androgen-dependent and androgen-independent prostate cancer cells.

Dorai T, Gehani N, Katz A. *Prostate Cancer Prostatic Dis* 2000;3:84-93.

In an effort to find an alternative nontoxic means of inducing the apoptosis potential in both androgen-dependent and hormone refractory prostate cancer cells, attention was focused on curcumin (turmeric), traditionally used in medicine and cuisine in India and other south-east Asian countries. The results indicate that curcumin is a novel and potent inducer of apoptosis in both androgen-dependent and androgen-independent prostate cancer cells. This was accomplished by down-regulating apoptosis suppressor proteins and other crucial proteins such as the androgen receptor. It is concluded that curcumin may provide an alternative, nontoxic modality by which the clinician may prevent the progression of prostate cancer to its hormone refractory state or to treat advanced prostate cancer by forcing them to undergo apoptosis.

Improvement of periodontal status by green tea catechin using a local delivery system: A clinical pilot study.

Hirasawa M, Takada K, Makimura M, Otake S. *J Periodontal Res* 2002;37:433-438.

The purpose of this study was to determine the usefulness of green tea catechin for the improvement of periodontal disease. The minimum inhibitory concentration (MIC) and bactericidal activity of green tea catechin against black-pigmented, Gram-negative anaerobic rods (BPR) were measured. Hydroxypropylcellulose strips containing green tea catechin as a slow release local delivery system were applied in pockets in patients once a week for 8 weeks. The clinical, enzymatic and microbiological effects of the catechin were determined. Green tea catechin showed a bactericidal effect against *Porphyromonas gingivalis* and *Prevotella* spp. in vitro with an MIC of 1.0 mg/ml. In the in vivo experiment, the pocket depth (PD) and the proportion of BPR were markedly decreased in the catechin group with mechanical treatment at week 8 compared with the baseline with significant difference. In contrast, PD and BPR were similar to the baseline and the value at the end of the experimental period in the placebo sites of scaled groups. The peptidase activities in the gingival fluid were maintained at lower levels during the experimental period in the test sites, while it reached 70% of that at baseline in the placebo sites. No morbidity was observed in the placebo and catechin groups without mechanical treatment. Green tea catechin showed a bactericidal effect against BPR and the combined use of mechanical treatment and the application of green tea catechin using a slow release local delivery system was effective in improving periodontal status.

Molecular mechanisms of in vivo metal chelation: implications for clinical treatment of metal intoxications.

Andersen O, Aaseth J. *Environ Health Perspect* 2002;110:S887-S890.

Successful in vivo chelation treatment of metal intoxication requires that a significant fraction of the administered chelator in fact chelate the toxic metal. This depends on metal, chelator, and organism-related factors (e.g., ionic diameter, ring size and deformability, hardness/softness of electron donors and acceptors, route of administration, bioavailability, metabolism, organ and intra/extracellular compartmentalization, and excretion). In vivo chelation is not necessarily an equilibrium reaction, determined by the standard stability constant, because rate effects and ligand exchange reactions considerably influence complex formation. Hydrophilic chelators most effectively promote renal metal excretion, but they complex intracellular metal deposits inefficiently. Lipophilic chelators can decrease intracellular stores but may redistribute toxic metals to, for example, the brain. In chronic metal-induced disease, where life-long chelation may be necessary, possible toxicity or side effects of the administered chelator may be limiting. The metal selectivity of chelators is important because of the risk of depletion of the patient's stores of essential metals. Dimercaptosuccinic acid and dimercaptopropionic sulfonate have gained more general acceptance among clinicians, undoubtedly improving the management of many human metal intoxications, including lead, arsenic, and mercury compounds. Still, development of new safer chelators suited for long-term oral administration for chelation of metal deposits (mainly iron), is an important research challenge for the future.