

LE Magazine October 2001

## ABSTRACTS

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## Theanine

Inhibition of glutamate transporter by theanine enhances the therapeutic efficacy of doxorubicin.

Theanine, a major amino acid existing in green tea, enhanced the antitumor activity of doxorubicin (DOX) due to inhibition of DOX efflux from tumor cells. In order to clarify the mechanism, we have investigated the contribution of glutamate transporters to the action of theanine, because theanine is a glutamate analogue. In M5076 ovarian sarcoma cells, glutamate transport inhibitors reduced the efflux of DOX, as well as theanine. Incidentally, theanine significantly inhibited the glutamate uptake by M5076 cells in a concentration-dependent manner similar to specific inhibitors. These results suggested that the inhibition of DOX efflux was induced by the inhibition of glutamate transport by theanine. In addition, RT-PCR and Western blot analysis revealed the expression of GLAST and GLT-1, astrocytic high-affinity glutamate transporters, in M5076 cells. Thus, theanine was shown to competitively inhibit the glutamate uptake by acting on these glutamate transporters. This action suggested the contribution of glutamate transporters to the inhibition of DOX efflux by theanine. We revealed the novel mechanism of enhancement of the antitumor efficacy of DOX via the inhibition of glutamate transporters by theanine.

Toxicol Lett 2001 Apr 30;121(2):89-96

Improvement of idarubicin induced antitumor activity and bone marrow suppression by theanine, a component of tea.

We have examined the effect of theanine, a specific amino acid in green tea, on idarubicin (IDA)-induced antitumor activity and toxicity. In combination with theanine, IDA (0.25 mg/kg per day x4 days, a dose that does not show antitumor activity) had significant antitumor activity in P388-bearing mice. The IDA concentration in the tumors in the theanine plus IDA group increased to twice the level in the IDA alone group. Furthermore, the decrease in tumor weight caused by IDA at 1.0 mg/kg per day x4 days (at this dose IDA exhibits antitumor activity) was significantly amplified by theanine. The numbers of leukocyte and bone marrow cells decreased significantly on IDA injection. Theanine significantly reversed these changes. These results suggest that theanine selectively moderates the IDA-induced toxicities. Until recently, the antitumor activity and related toxicities of this chemotherapeutic agent in leukemia could not be distinguished. Theanine increases the IDA-induced antitumor activity and ameliorates the toxicities.

Cancer Lett 2000 Oct 1;158(2):119-24

Inhibiting effects of theanine on caffeine stimulation evaluated by EEG in the rat.

In this study, the inhibiting action of theanine on the excitation by caffeine at the concentration regularly associated with drinking tea was investigated using electroencephalography (EEG) in rats. First, the stimulatory action by caffeine i.v. administration at a level higher than 5 micromol/kg (0.970 mg/kg) b.w. was shown by means of brain wave analysis, and this level was suggested as the minimum dose of caffeine as a stimulant. Next, the stimulatory effects of caffeine were inhibited by an i.v. administration of theanine at a level higher than 5 micromol/kg (0.781 mg/kg) b.w., and the results suggested that theanine has an antagonistic effect on caffeine's stimulatory action at an almost equivalent molar concentration. On the other hand, the excitatory effects were shown in the rat i.v. administered 1 and 2 micromol/kg (0.174 and 0.348 mg/kg) b.w. of theanine alone. These results suggested two effects of theanine, depending on its concentration.

Biosci Biotechnol Biochem 2000 Feb;64(2):287-93

Mortality among female practitioners of Chanoyu-Japanese tea-ceremony.

A cohort study aimed to evaluate the effect of drinking green tea on longevity was performed. Three thousand three hundred and eighty female practitioners of chanoyu (Japanese tea-ceremony), living in Tokyo, were followed from 1980 to 1988, and 280 were dead during this period. Standardized mortality ratios were estimated 0.55 when all Japanese women was used as standard

population and 0.57 when women living in Tokyo was used, indicating the possibility that green tea is a protective factor for several fatal diseases.

Tohoku J Exp Med 1992 Apr;166(4):475-7

Protective effect of gamma-glutamylethylamide (theanine) on ischemic delayed neuronal death in gerbils.

We examined the protective effect of gamma-glutamylethylamide (theanine) on ischemic delayed neuronal death in field CA1 of the gerbil hippocampus. One microliter of theanine from each three concentrations (50, 125 and 500 microM) was administered through the lateral ventricle 30 min before ischemia. Transient forebrain ischemia was induced by bilateral occlusion of the common carotid arteries for 3 min under careful control of brain temperature at approximately 37 degrees C. Seven days after ischemia, the number of intact CA1 neurons in the hippocampus was assessed. Ischemia-induced neuronal death in hippocampal CA1 region was significantly prevented in a dose-dependent manner in the theanine-pretreated groups. These findings indicate that theanine might be useful clinically for preventing ischemic neuronal damage.

Neurosci Lett 2000 Aug 11;289(3):189-92

Coffee and tea intake and the risk of myocardial infarction.

The authors investigated the association of caffeinated coffee, decaffeinated coffee, and tea with myocardial infarction in a study of 340 cases and age-, sex-, and community-matched controls. The odds ratio for drinking > or = 4 cups/day of caffeinated coffee versus drinking < or = 1 cup/week was 0.84 (95% confidence interval (CI) 0.49-1.42) after adjustment for coronary risk factors (1 cup = 237 ml). The odds ratio for drinking > 1 cup/day of decaffeinated coffee versus nondrinkers was 1.25 (95% CI 0.76-2.04). For tea, the odds ratio for drinking > or = 1 cup/day versus nondrinkers was 0.56 (95% CI 0.35-0.90). In these data, only tea was associated with a lower risk of myocardial infarction.

Am J Epidemiol 1999 Jan 15;149(2):162-7

Hypotensive effect of gamma-glutamylmethylamide in spontaneously hypertensive rats.

The effect of gamma-glutamylmethylamide(GMA), one of the components of green tea extract, on the blood pressure in spontaneously hypertensive rats (SHR) was investigated. The effect of glutamic acid and r-glutamylethylamide (theanine), which is structurally similar to GMA, was also examined. When SHR were injected with glutamic acid (2000mg/kg), the blood pressure was not altered. The same dose of theanine decreased it significantly. GMA administration to SHR reduced the blood pressure significantly, and its degree of hypotensive action was more effective than that by theanine administration.

Life Sci 1998;62(12):1065-8

Reduction effect of theanine on blood pressure and brain 5-hydroxyindoles in spontaneously hypertensive rats.

The effect of theanine, one of the components of green tea, on the blood pressure and brain 5-hydroxyindoles in spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY) was investigated by intraperitoneally administering theanine. The effect of glutamine, which is structurally similar to theanine, was also examined. When SHR were injected with various amounts of theanine (0, 500, 1000, 1500 and 2000 mg/kg), the change was dose-dependent, and a significant decrease in blood pressure was observed with the high doses (1500 and 2000 mg/kg). A dose of 2000 mg/kg of theanine did not alter the blood pressure of WKY, while the same dose to SHR decreased it significantly. On the other hand, glutamine administration to SHR did not change either the blood pressure or the heart rate. The brain 5-hydroxyindole level was significantly decreased by theanine administration to both WKY and SHR, the decrease being dose-dependent.

Biosci Biotechnol Biochem 1995 Apr;59(4):615-8

CoQ10

Coenzyme Q10 improves mitochondrial respiration in patients with mitochondrial cytopathies. An in vivo study on brain and skeletal muscle by phosphorous magnetic resonance spectroscopy.

With phosphorus magnetic resonance spectroscopy (31P-MRS) we studied in vivo the effect of six-month coenzyme Q10 treatment on the efficiency of brain and skeletal muscle mitochondrial respiration in six patients with different mitochondrial cytopathies. Before CoQ10 we found a low phosphocreatine content (average of 25% decrease from controls) in the occipital lobes of all patients. Calculated [ADP] and the relative rate of ATP synthesis were high (as an average, 57% and 16% above control group respectively), whereas the cytosolic phosphorylation potential was low (as an average, 60% of control value). 31P-MRS also

revealed an average of 29% reduction of the mitochondrial function in the skeletal muscle of patients compared with controls. After a six-month treatment with 150 mg CoQ10/day all brain variables were remarkably improved in all patients, returning within the control range in all cases. Treatment with CoQ10 also improved the muscle mitochondrial functionality enough to reduce the average deficit to 56% of the control group. These in vivo findings show the beneficial effect of CoQ10 in patients with mitochondrial cytopathies, and are consistent with the view that increased CoQ10 concentration in the mitochondrial membrane increases the efficiency of oxidative phosphorylation independently of enzyme deficit.

Cell Mol Biol 1997 Jul;43(5):741-9

Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects.

Coenzyme Q10 is an essential cofactor of the electron transport chain as well as a potent free radical scavenger in lipid and mitochondrial membranes. Feeding with coenzyme Q10 increased cerebral cortex concentrations in 12- and 24-month-old rats. In 12-month-old rats administration of coenzyme Q10 resulted in significant increases in cerebral cortex mitochondrial concentrations of coenzyme Q10. Oral administration of coenzyme Q10 markedly attenuated striatal lesions produced by systemic administration of 3-nitropropionic acid and significantly increased life span in a transgenic mouse model of familial amyotrophic lateral sclerosis. These results show that oral administration of coenzyme Q10 increases both brain and brain mitochondrial concentrations. They provide further evidence that coenzyme Q10 can exert neuroprotective effects that might be useful in the treatment of neurodegenerative diseases.

Proc Natl Acad Sci U S A 1998 Jul 21;95(15):8892-7

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Mitochondrial encephalomyopathy with coenzyme Q10 deficiency.

Coenzyme Q10 (CoQ10) transfers electrons from complexes I and II of the mitochondrial respiratory chain to complex III. There is one published report of human CoQ10 deficiency describing two sisters with encephalopathy, proximal weakness, myoglobinuria and lactic acidosis. We report a patient who had delayed motor milestones, proximal weakness, premature exertional fatigue and episodes of exercise-induced pigmenturia. She also developed partial-complex seizures. Serum creatine kinase was approximately four times the upper limit of normal and venous lactate was mildly elevated. Skeletal muscle biopsy revealed many ragged-red fibers, cytochrome c oxidase-deficient fibers and excess lipid. In isolated muscle mitochondria, impaired oxygen consumption was corrected by the addition of decylubiquinone. During standardized exercise, ventilatory and circulatory responses were compatible with a defect of oxidation-phosphorylation, which was confirmed by near-infrared spectroscopy analysis. Biochemical analysis of muscle extracts revealed decreased activities of complexes I+II and I+III, while CoQ10 concentration was less than 25% of normal. With a brief course of CoQ10 (150 mg daily), the patient reported subjective improvement. The triad of CNS involvement, recurrent myoglobinuria, and ragged-red fibers should alert clinicians to the possibility of CoQ10 deficiency.

Neurology 1997 May;48(5):1238-43

Control of arterial tone after long-term coenzyme Q10 supplementation in senescent rats.

1. Age-associated deterioration of arterial function may result from long-lasting oxidative stress. Since coenzyme Q (Q10) has been suggested to protect the vascular endothelium from free radical-induced damage, we investigated the effects of long-term dietary Q10 supplementation on arterial function in senescent Wistar rats. 2. At 16 months of age, 18 rats were divided into two groups. The control group was kept on a standard diet while the other group was supplemented with Q10 (10 mg kg<sup>-1</sup> day<sup>-1</sup>). In addition, nine rats (age 2 months) also ingesting a standard diet were used as the young control group. After 8 study weeks the responses of the mesenteric arterial rings in vitro were examined. 3. Endothelium-independent arterial relaxations to isoprenaline and nitroprusside (SNP) were attenuated in aged rats. Increased dietary Q10 clearly enhanced the relaxation to isoprenaline, but did not affect the response to SNP. In addition, vasodilation of noradrenaline-precontracted rings to acetylcholine (ACh), which was also impaired in aged vessels, was improved after Q10 supplementation. Cyclooxygenase inhibition with diclofenac enhanced the relaxation to ACh only in young rats, while it abolished the difference between the old controls and Q10 supplemented rats, suggesting that the improved endothelium-dependent vasodilation observed in Q10 supplemented rats was largely mediated by prostacyclin (PGI<sub>2</sub>). 4. In conclusion, long-term Q10 supplementation improved endothelium-dependent vasodilation and enhanced beta-adrenoceptor-mediated arterial relaxation in senescent Wistar rats. The mechanisms underlying the improvement of endothelial function may have included augmented endothelial production of PGI<sub>2</sub>, increased sensitivity of smooth muscle to PGI<sub>2</sub> or both.

Br J Pharmacol 1998 Aug;124(7):1500-6

Oral coenzyme Q10 administration prevents the development of ischemic brain lesions in a rabbit model of symptomatic vasospasm.

Treatment with oral coenzyme Q10 (CoQ10, 10 mg/kg per day for 6 days) was compared with no treatment in a previously described rabbit model of symptomatic cerebral vasospasm [Endo et al. (1988) Stroke 19: 1420-1425]. The treatment was initiated within 1-2 h after injection of autologous blood into the subarachnoid space. In CoQ10-untreated rabbits, moderate to severe neurological deficits developed, and multiple focal ischemic lesions were found in the brain regions with compromised blood supply, i.e., in the regions normally supplied by common carotid arteries which are subject to ligation in this model. CoQ10 treatment prevented the development of both the neurological deficits and histologically detectable brain tissue damage. In both CoQ10-treated and -untreated rabbits, infiltration of mononuclear cells was evident in the brain stem, although this region did not show signs of ischemic damage. The findings indicate that the histological and neurological correlates of brain tissue damage in this rabbit model of symptomatic cerebral vasospasm develop via mechanism(s) involving free radical-mediated oxidation of plasma lipoproteins. Similar mechanisms may play a role in the development of brain damage attributed to cerebral atherosclerosis.

Acta Neuropathol (Berl) 1997 Oct;94(4):363-8

Ubiquinone (coenzyme q10) and mitochondria in oxidative stress of Parkinson's disease.

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease affecting approximately 1% of the population older than 50 years. There is a worldwide increase in disease prevalence due to the increasing age of human populations. A definitive neuropathological diagnosis of Parkinson's disease requires loss of dopaminergic neurons in the substantia nigra and related brain stem nuclei, and the presence of Lewy bodies in remaining nerve cells. The contribution of genetic factors to the pathogenesis of Parkinson's disease is increasingly being recognized. A point mutation which is sufficient to cause a rare autosomal dominant form of the disorder has been recently identified in the alpha-synuclein gene on chromosome 4 in the much more common sporadic, or 'idiopathic' form of Parkinson's disease, and a defect of complex I of the mitochondrial respiratory chain was confirmed at the biochemical level. Disease specificity of this defect has been demonstrated for the parkinsonian substantia nigra. These findings and the observation that the neurotoxin 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP), which causes a Parkinson-like syndrome in humans, acts via inhibition of complex I have triggered research interest in the mitochondrial genetics of Parkinson's disease. Oxidative phosphorylation consists of five protein-lipid enzyme complexes located in the mitochondrial inner membrane that contain flavins (FMN, FAD), quinoid compounds (coenzyme Q10, CoQ10) and transition metal compounds (iron-sulfur clusters, hemes, protein-bound copper). These enzymes are designated complex I (NADH:ubiquinone oxidoreductase, EC 1.6. 5.3), complex II (succinate:ubiquinone oxidoreductase, EC 1.3.5.1), complex III (ubiquinol:ferrocycytochrome c oxidoreductase, EC 1.10.2.2), complex IV (ferrocycytochrome c: oxygen oxidoreductase or cytochrome c oxidase, EC 1.9.3.1), and complex V (ATP synthase, EC 3.6.1.34). A defect in mitochondrial oxidative phosphorylation, in terms of a reduction in the activity of NADH CoQ reductase (complex I) has been reported in the striatum of patients with Parkinson's disease. The reduction in the activity of complex I is found in the substantia nigra, but not in other areas of the brain, such as globus pallidus or cerebral cortex. Therefore, the specificity of mitochondrial impairment may play a role in the degeneration of nigrostriatal dopaminergic neurons. This view is supported by the fact that MPTP generating 1-methyl-4-phenylpyridine (MPP(+)) destroys dopaminergic neurons in the substantia nigra. Although the serum levels of CoQ10 is normal in patients with Parkinson's disease, CoQ10 is able to attenuate the MPTP-induced loss of striatal dopaminergic neurons.

Biol Signals Recept 2001 May-Aug;10(3-4):224-53

Two successful double-blind trials with coenzyme Q10 (vitamin Q10) on muscular dystrophies and neurogenic atrophies.

Coenzyme Q10 (vitamin Q10) is biosynthesized in the human body and is functional in bioenergetics, anti-oxidation reactions, and in growth control, etc. It is indispensable to health and survival. The first double-blind trial was with twelve patients, ranging from 7 to 69 years of age, having diseases including the Duchenne, Becker, and the limb-girdle dystrophies, myotonic dystrophy, Charcot-Marie-Tooth disease, and the Welander disease. The control coenzyme Q10 (CoQ10) blood level was low and ranged from 0.5 to 0.84 microgram/ml. They were treated for three months with 100 mg daily of CoQ10 and a matching placebo. The second double-blind trial was similar with fifteen patients having the same categories of disease. Since cardiac disease is established to be associated with these muscle diseases, cardiac function was blindly monitored, and not one mistake was made in assigning CoQ10 and placebo to the patients in both trials. Definitely improved physical performance was recorded. In retrospect, a dosage of 100 mg was too low although effective and safe. Patients suffering from these muscle dystrophies and the like, should be treated with vitamin Q10 indefinitely.

Biochim Biophys Acta 1995 May 24;1271(1):281-6

Coenzyme Q10 and nicotinamide block striatal lesions produced by the mitochondrial toxin malonate.

A potential mechanism of neuronal injury in neurodegenerative diseases is a defect in energy metabolism that may lead to slow excitotoxic neuronal death. Consistent with this possibility, we showed that specific inhibitors of the electron transport chain produce excitotoxic lesions in vivo. In the present study we examined whether agents that improve energy metabolism can block lesions produced by the mitochondrial toxin malonate. Striatal lesions produced by the complex II inhibitor malonate were blocked in a dose-dependent manner by oral pretreatment with coenzyme Q10. Administration of nicotinamide by Alzet pump for 1 week attenuated malonate-induced lesions, but riboflavin had no effect. Administration of nicotinamide intraperitoneally just prior to and following induction of the lesions produced dose-dependent neuroprotection. A combination of coenzyme Q10 with nicotinamide was more effective than either compound alone, as shown by both lesion size and magnetic resonance imaging in vivo. Both coenzyme Q10 and nicotinamide blocked adenosine triphosphate depletions and lactate increases. These results confirm that mitochondrial toxins produce striatal excitotoxic lesions by a mechanism involving energy depletion in vivo. Furthermore, they suggest novel neuroprotective strategies that may be useful in the treatment of both mitochondrial encephalopathies and neurodegenerative diseases.

Ann Neurol 1994 Dec;36(6):882-8

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## ABSTRACTS

## Green Tea/Cancer

Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols.

Development of effective chemopreventive agents against prostate cancer (CaP) for humans requires conclusive evidence of their efficacy in animal models that closely emulates human disease. The autochthonous transgenic adenocarcinoma of the mouse prostate (TRAMP) model, which spontaneously develops metastatic CaP, is one such model that mimics progressive forms of human disease. Employing male TRAMP mice, we show that oral infusion of a polyphenolic fraction isolated from green tea (GTP) at a human achievable dose (equivalent to six cups of green tea per day) significantly inhibits CaP development and increases survival in these mice. In two separate experiments, the cumulative incidence of palpable tumors at 32 weeks of age in 20 untreated mice was 100% (20 of 20). In these mice, 95% (19 of 20), 65% (13 of 20), 40% (8 of 20), and 25% (5 of 20) of the animals exhibited distant site metastases to lymph nodes, lungs, liver, and bone, respectively. However, 0.1% GTP (wt/vol) provided as the sole source of drinking fluid to TRAMP mice from 8 to 32 weeks of age resulted in (i) significant delay in primary tumor incidence and tumor burden as assessed sequentially by MRI, (ii) significant decrease in prostate (64%) and genitourinary (GU) (72%) weight, (iii) significant inhibition in serum insulin-like growth factor-I and restoration of insulin-like growth factor binding protein-3 levels, and (iv) marked reduction in the protein expression of proliferating cell nuclear antigen (PCNA) in the prostate compared with water-fed TRAMP mice. The striking observation of this study was that GTP infusion resulted in almost complete inhibition of distant site metastases. Furthermore, GTP consumption caused significant apoptosis of CaP cells, which possibly resulted in reduced dissemination of cancer cells, thereby causing inhibition of prostate cancer development, progression, and metastasis of CaP to distant organ sites.

Proc Natl Acad Sci U S A 2001 Aug 14

Green tea extracts decrease carcinogen-induced mammary tumor burden in rats and rate of breast cancer cell proliferation in culture.

Epidemiological evidence suggests tea (*Camellia sinensis* L.) has chemopreventive effects against various tumors. Green tea contains many polyphenols, including epigallocatechin-3 gallate (EGCG), which possess anti-oxidant qualities. Reduction of chemically induced mammary gland carcinogenesis by green tea in a carcinogen-induced rat model has been suggested previously, but the results reported were not statistically significant. Here we have tested the effects of green tea on mammary tumorigenesis using the 7,12-dimethylbenz(a)anthracene (DMBA) Sprague-Dawley (S-D) rat model. We report that green tea significantly increased mean latency to first tumor, and reduced tumor burden and number of invasive tumors per tumor-bearing animal; although, it did not affect tumor number in the female rats. Furthermore, we show that proliferation and/or viability of cultured Hs578T and MDA-MB-231 estrogen receptor-negative breast cancer cell lines was reduced by EGCG treatment. Similar negative effects on proliferation were observed with the DMBA-transformed D3-1 cell line. Growth inhibition of Hs578T cells correlated with induction of p27(Kip1) cyclin-dependent kinase inhibitor (CKI) expression. Hs578T cells expressing elevated levels of p27(Kip1) protein due to stable ectopic expression displayed increased G1 arrest. Thus, green tea had significant chemopreventive effects on carcinogen-induced mammary tumorigenesis in female S-D rats. In culture, inhibition of human breast cancer cell proliferation by EGCG was mediated in part via induction of the p27(Kip1) CKI.

J Cell Biochem 2001;82(3):387-98

Inhibitory effects of orally administered green tea, black tea, and caffeine on skin carcinogenesis in mice previously treated with ultraviolet B light (high-risk mice): relationship to decreased tissue fat.

Treatment of SKH-1 hairless mice with ultraviolet B light (UVB; 30 mJ/cm<sup>2</sup>) twice a week for 22 weeks resulted in tumor-free animals with a high risk of developing malignant and nonmalignant skin tumors during the next several months in the absence of additional UVB treatment (high-risk mice). Oral administration of green tea or black tea (6 mg tea solids/ml) to UVB-pretreated high-risk SKH-1 mice for 23 weeks after stopping UVB treatment decreased the number of tumors/mouse, decreased the size of the parametrial fat pads, and decreased the thickness of the dermal fat layer away from tumors and directly under tumors. Administration of the decaffeinated teas had little or no effect on these parameters, and adding caffeine (equivalent to the amount in the regular teas) to the decaffeinated teas restored their inhibitory effects. Administration of caffeine alone also decreased the number of tumors/mouse, the size of the parametrial fat pads, and the thickness of the dermal fat layer away from tumors and under tumors. Using data from individual mice and linear regression and correlation analysis, we found a highly significant positive

correlation between the thickness of the dermal fat layer away from tumors and the number of tumors/mouse ( $r = 0.34$ ;  $P = 0.0001$ ), but the correlation between average tumor size/mouse and the thickness of the dermal fat layer away from tumors was weak ( $r = 0.16$ ;  $P = 0.034$ ). The results suggested that p.o. administered tea or caffeine may have decreased tumor multiplicity in part by decreasing fat levels in the dermis. Additional analysis revealed that oral administration of caffeinated beverages (green tea, black tea, decaffeinated green tea plus caffeine, decaffeinated black tea plus caffeine, or caffeine alone) decreased the thickness of the dermal fat layer under large tumors to a much greater extent than under small tumors. This is the first demonstration of a close association between inhibition of carcinogenesis and the lowering of tissue fat levels by a chemopreventive agent.

Cancer Res 2001 Jul 1;61(13):5002-9

Intake of butylated hydroxyanisole and butylated hydroxytoluene and stomach cancer risk: results from analyses in the Netherlands Cohort Study.

Both carcinogenic and anticarcinogenic properties have been reported for the synthetic antioxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). The association between dietary intake of BHA and BHT and stomach cancer risk was investigated in the Netherlands Cohort Study (NLCS) that started in 1986 among 120,852 men and women aged 55 to 69 years. A semi-quantitative food frequency questionnaire was used to assess food consumption. Information on BHA or BHT content of cooking fats, oils, mayonnaise and other creamy salad dressings and dried soups was obtained by chemical analysis, a Dutch database of food additives (ALBA) and the Dutch Compendium of Foods and Diet Products. After 6.3 years of follow-up, complete data on BHA and BHT intake of 192 incident stomach cancer cases and 2035 subcohort members were available for case-cohort analysis. Mean intake of BHA or BHT among subcohort members was 105 and 351 microg/day, respectively. For consumption of mayonnaise and other creamy salad dressings with BHA or BHT no association with stomach cancer risk was observed. A statistically non-significant decrease in stomach cancer risk was observed with increasing BHA and BHT intake [rate ratio (RR) highest/lowest intake of BHA = 0.57 (95% confidence interval (CI): 0.25-1.30) and BHT = 0.74 (95% CI: 0.38-1.43)]. In this study, no significant association with stomach cancer risk was found for usual intake of low levels of BHA and BHT.

Food Chem Toxicol 2000 Jul;38(7):599-605

Stomach cancer-related mortality.

In Japan stomach cancer remains the leading cause of cancer-related mortality. We analyzed the annual mortality rate of stomach cancer in relation to age, gender and life expectancy in Japan between 1970 and 1995. The adjusted stomach cancer-related mortality rates decreased from 88.9 in 1970 to 45.4 per 100,000 in 1995 in males and from 46.5 to 18.5 per 100,000 in females. The male-female ratio for stomach cancer-related mortality in all ages was 1.9 to 2.5 during this 25-year period, and the mortality rate was higher in females than in males at young age. The negative contribution to life expectancy for stomach cancer in males was 0.65 years and 0.42 years in females, which is consistent with a higher mortality rate in males. This negative contribution was 41.8% of total cancer in 1970 and 39.4% in 1995 in males and 34.4% and 16.0%, respectively, in females. Our results demonstrated the need to take into consideration the characteristics of stomach cancer in young women and the effects of aging when designing programs aimed at prevention and control of this malignancy.

Eur J Cancer Prev 2001 Feb;10(1):61-7

Green tea and the risk of gastric cancer in Japan.

**BACKGROUND:** Although laboratory experiments and case-control studies have suggested that the consumption of green tea provides protection against gastric cancer, few prospective studies have been performed. **METHODS:** In January 1984, a total of 26,311 residents in three municipalities of Miyagi Prefecture, in northern Japan (11,902 men and 14,409 women 40 years of age or older), completed a self-administered questionnaire that included questions about the frequency of consumption of green tea. During 199,748 person-years of follow-up, through December 1992, we identified 419 cases of gastric cancer (in 296 men and 123 women). We used Cox regression to estimate the relative risk of gastric cancer according to the consumption of green tea. **RESULTS:** Green-tea consumption was not associated with the risk of gastric cancer. After adjustment for sex, age, presence or absence of a history of peptic ulcer smoking status, alcohol consumption, other dietary elements, and type of health insurance, the relative risks associated with drinking one or two, three or four, and five or more cups of green tea per day, as compared with less than one cup per day, were 1.1 (95 percent confidence interval, 0.8 to 1.6), 1.0 (95 percent confidence interval, 0.7 to 1.4), and 1.2 (95 percent confidence interval, 0.9 to 1.6), respectively ( $P$  for trend=0.13). The results were similar after the 117 cases of gastric cancer that were diagnosed in the first three years of follow-up had been excluded, with respective relative risks of 1.2 (95 percent confidence interval, 0.8 to 1.8) 1.0 (95 percent confidence interval, 0.7 to 1.5), and 1.4 (95 percent confidence interval, 1.0 to 1.9) ( $P$  for trend=0.07). **CONCLUSIONS:** In a population-based, prospective cohort study in Japan, we found no association between green-tea consumption and the risk of gastric cancer.

N Engl J Med 2001 Mar 1;344(9):632-6

Nitrosamines have been suspected in the etiology of esophageal/ gastric cardia cancer in the high incidence area of Linxian of the Henan Province in northern China, but marginal deficiencies in riboflavin, vitamins A and C, and other micronutrients may also be involved. A joint U.S.-China nutritional intervention study with investigators from the Cancer Institute of the Chinese Academy of Medical Sciences and the U.S. National Cancer Institute tested the effects of the following four combinations of nutrients on 29,584 subjects in an eight-group design: 1) retinol and zinc; 2) riboflavin and niacin; 3) vitamin C and molybdenum; and 4) vitamin E, beta-carotene and selenium. Supplementation with Group 4 nutrients significantly decreased mortality rate from stomach cancer, primarily due to the decrease in deaths resulting from adenocarcinomas of the gastric cardia; it lowered the total mortality rate and showed signs of other beneficial effects. Another study of nutrition and gastric cancer in a high incidence area of Linqu of the Shangdong province in northern China (in collaboration with the Beijing Institute for Cancer Research and the U. S. National Institutes of Health) found significantly lower serum concentrations of vitamin C and beta-carotene among individuals with intestinal metaplasia; an intervention trial with vitamins C and E and selenium (combined) is ongoing in Linqu. Other studies are also elucidating the mechanisms for the pathogenesis of adenocarcinoma at the gastroesophageal junction with the use of a rat model. Such studies are expected to shed light on the etiology and prevention of gastroesophageal cancers in humans.

J Nutr 2000 Feb;130(2S Suppl):338S-339S

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### Micronutrients

DNA damage from micronutrient deficiencies is likely to be a major cause of cancer.

A deficiency of any of the micronutrients: folic acid, vitamin B12, vitamin B6, niacin, vitamin C, vitamin E, iron or zinc, mimics radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions or both. For example, the percentage of the US population that has a low intake (<50% of the RDA) for each of these eight micronutrients ranges from 2 to >20%. A level of folate deficiency causing chromosome breaks was present in approximately 10% of the US population, and in a much higher percentage of the poor. Folate deficiency causes extensive incorporation of uracil into human DNA (4 million/cell), leading to chromosomal breaks. This mechanism is the likely cause of the increased colon cancer risk associated with low folate intake. Some evidence, and mechanistic considerations, suggest that vitamin B12 (14% US elderly) and B6 (10% of US) deficiencies also cause high uracil and chromosome breaks. Micronutrient deficiency may explain, in good part, why the quarter of the population that eats the fewest fruits and vegetables (five portions a day is advised) has about double the cancer rate for most types of cancer when compared to the quarter with the highest intake. For example, 80% of American children and adolescents and 68% of adults do not eat five portions a day. Common micronutrient deficiencies are likely to damage DNA by the same mechanism as radiation and many chemicals, appear to be orders of magnitude more important, and should be compared for perspective. Remedying micronutrient deficiencies should lead to a major improvement in health and an increase in longevity at low cost.

Mutat Res 2001 Apr 18;475(1-2):7-20

### Chronic heart failure and micronutrients.

Heart failure (HF) is associated with weight loss, and cachexia is a well-recognized complication. Patients have an increased risk of osteoporosis and lose muscle bulk early in the course of the disease. Basal metabolic rate is increased in HF, but general malnutrition may play a part in the development of cachexia, particularly in an elderly population. There is evidence for a possible role for micronutrient deficiency in HF. Selective deficiency of selenium, calcium and thiamine can directly lead to the HF syndrome. Other nutrients, particularly vitamins C and E and beta-carotene, are antioxidants and may have a protective effect on the vasculature. Vitamins B6, B12 and folate all tend to reduce levels of homocysteine, which is associated with increased oxidative stress. Carnitine, coenzyme Q10 and creatine supplementation have resulted in improved exercise capacity in patients with HF in some studies. In this article, we review the relation between micronutrients and HF. Chronic HF is characterized by high mortality and morbidity, and research effort has centered on pharmacological management, with the successful introduction of angiotensin-converting enzyme inhibitors and beta-adrenergic antagonists into routine practice. There is sufficient evidence to support a large-scale trial of dietary micronutrient supplementation in HF.

J Am Coll Cardiol 2001 Jun 1;37(7):1765-74

### Host selenium status selectively influences susceptibility to experimental viral myocarditis.

The purpose of the present work was to determine whether dietary selenium (Se) deficiency could influence the injurious effect of human viruses other than Coxsackie virus B3 (CVB3) on mouse heart. Weanling C3H/HeN mice were fed a Se-deficient or Se-adequate diet for 4 wk and then were inoculated intraperitoneally with one of the following viruses: Coxsackie virus B1 (CVB1), echovirus 9 (EV9), Coxsackie virus A9 (CVA9), or herpes simplex 1 (HSV1). Polio virus 1 (PV1) was employed as a negative control. Prior to inoculation, mean serum Se levels were 430 versus 61 ng/mL in adequate versus deficient mice, respectively. Ten days later, hearts were removed and processed by routine histological procedures. Cardiac lesions were scored according to the number and size of myocarditic foci. Significantly greater heart damage resulting from CVB1 and EV9 was observed in Se-deficient than in Se-adequate mice, and the Se status had no influence on CVA9-induced myocarditis. In contrast, heart damage caused by HSV1 was significantly milder in Se-deficient than in Se-adequate mice. Therefore, it may be concluded that the Se status of the murine host selectively influences the degree of viral-induced myocarditic lesions.

Biol Trace Elem Res 2001 Apr;80(1):23-31

### Selenium deficiency is associated with shedding of HIV-1—infected cells in the female genital tract.

**OBJECTIVE:** To assess the relation between selenium deficiency and vaginal or cervical shedding of HIV-1-infected cells. **DESIGN:** Cross-sectional study of 318 HIV-1 seropositive women in Mombasa, Kenya. **METHODS:** Vaginal and cervical swab specimens were tested for the presence of HIV-1 DNA by polymerase chain reaction. Multivariate logistic regression models, adjusting for CD4 count and vitamin A deficiency, were used. **RESULTS:** Selenium deficiency (defined as levels <85 microg/L) was observed in 11% of the study population. In unstratified multivariate analyses, there was no significant association between selenium deficiency and vaginal or cervical shedding. In stratified analyses, however, significant associations became apparent after excluding women with predictors of shedding with strong local effects on the genital tract mucosa. Among women who did not use oral contraceptives and who did not have vaginal candidiasis, selenium deficiency was significantly associated with vaginal shedding (adjusted odds ratio [AOR] 2.9, 95% confidence interval [CI] 1.0--8.8,  $p = .05$ ). Effect modification was also observed in the relation between selenium deficiency and cervical shedding, with a significant association seen among those women who were not using oral contraceptive pills or depot medroxyprogesterone acetate and who did not have *Neisseria gonorrhoeae* infection (AOR 2.8, 95% CI 1.1--7.0,  $p = .02$ ). **CONCLUSIONS:** We found selenium deficiency to be associated with a nearly threefold higher likelihood of genital mucosal shedding of HIV-1-infected cells, suggesting that deficiency may increase the infectiousness of women with HIV-1. Nutritional interventions to prevent HIV-1 transmission warrant investigation.

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Role of micronutrients in HIV-infected intravenous drug users.

Nutritional deficiencies are widespread among HIV-1-seropositive male and female drug abusers (injecting drug users, or IDUs), among men who have sex with men (MSM), and among children, although the prevalence of nutritional alterations varies among the groups. Low levels of vitamin A, vitamin B12, zinc and selenium are common and have been demonstrated to be associated with disease progression and HIV-1 related mortality, independent of CD4 count <200 cells/mm<sup>3</sup> at baseline and CD4 count over time. When all nutrient factors that are associated with survival are considered together, only selenium deficiency is a significant predictor of mortality. The profound effect of selenium on disease progression may reflect selenium's action in antioxidant defense systems, as well as gene regulation.

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A conservative triple antioxidant approach to the treatment of hepatitis C. Combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories.

**BACKGROUND:** There has been an increase in the number of adults seeking liver transplantation for hepatitis C in the last few years and the count is going up rapidly. There is no reliable and effective therapy for chronic hepatitis C since interferon and antivirals work no more than 30% of the time, and liver transplant surgery is uncertain and tentative over the long run. This is because, ultimately, residual hepatitis C viremia infects the new liver. Furthermore, liver transplantation can be painful, disabling and extremely costly. **TREATMENT PROGRAM:** The author describes a low cost and efficacious treatment program in 3 patients with cirrhosis, portal hypertension and esophageal varices secondary to chronic hepatitis C infection. This effective and conservative regimen combines 3 potent antioxidants (alpha-lipoic acid [thioctic acid], silymarin and selenium) that possess antiviral, free radical quenching and immune boosting qualities. **CONCLUSION:** There are no remarkably effective treatments for chronic hepatitis C in general use. Interferon and antivirals have less than a 30% response rate and because of the residual viremia, a newly transplanted liver usually becomes infected again. The triple antioxidant combination of alpha-lipoic acid, silymarin and selenium was chosen for a conservative treatment of hepatitis C because these substances protect the liver from free radical damage, increase the levels of other fundamental antioxidants, and interfere with viral proliferation. The 3 patients presented in this paper followed the triple antioxidant program and recovered quickly and their laboratory values remarkably improved. Furthermore, liver transplantation was avoided and the patients are back at work, carrying out their normal activities, and feeling healthy. The author offers a more conservative approach to the treatment of hepatitis C, that is exceedingly less expensive. One year of the triple antioxidant therapy described in this paper costs less than \$2,000, as compared to more than \$300,000 a year for liver transplant surgery. It appears reasonable, that prior to liver transplant surgery evaluation, or during the transplant evaluation process, the conservative triple antioxidant treatment approach should be considered. If these is a significant betterment in the patient's condition, liver transplant surgery may be avoided.

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Oxygenated carotenoid lutein and progression of early atherosclerosis: the Los Angeles atherosclerosis study.

**BACKGROUND:** Carotenoids are hypothesized to explain some of the protective effects of fruit and vegetable intake on risk of cardiovascular disease. The present study assessed the protective effects of the oxygenated carotenoid lutein against early atherosclerosis. **METHODS AND RESULTS:** Epidemiology: Progression of intima-media thickness (IMT) of the common carotid arteries over 18 months was determined ultrasonographically and was related to plasma lutein among a randomly sampled cohort of utility employees age 40 to 60 years ( $n=480$ ). Coculture: The impact of lutein on monocyte response to artery wall cell modification of LDL was assessed in vitro by quantification of monocyte migration in a coculture model of human intima. Mouse

models: The impact of lutein supplementation on atherosclerotic lesion formation was assessed in vivo by assigning apoE-null mice to chow or chow plus lutein (0.2% by weight) and LDL receptor-null mice to Western diet or Western diet plus lutein. IMT progression declined with increasing quintile of plasma lutein (P for trend=0.007, age-adjusted; P=0.0007, multivariate). Covariate-adjusted IMT progression (mean $\pm$ SEM) was 0.021 $\pm$ 0.005 mm in the lowest quintile of plasma lutein, whereas progression was blocked in the highest quintile (0.004 $\pm$ 0.005 mm; P=0.01). In the coculture, pretreatment of cells with lutein inhibited LDL-induced migration in a dose-dependent manner (P<0.05). Finally, in the mouse models, lutein supplementation reduced lesion size 44% in apoE-null mice (P=0.009) and 43% in LDL receptor-null mice (P=0.02). CONCLUSIONS: These epidemiological, in vitro, and mouse model findings support the hypothesis that increased dietary intake of lutein is protective against the development of early atherosclerosis.

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