

# Abstracts

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## Recently Published Abstracts

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### **A significant correlation between melatonin deficiency and endometrial cancer.**

Grin W, Grunberger W.  
*Gynecol Obstet Invest*  
1998;45:62-65.

Endometrial cancer is the most common pelvic genital cancer in women. Its incidence is increasing. Unlike the successful screening method for cervical cancer, there is no such equivalent procedure for the early diagnosis of endometrial cancer. Screening procedures currently being tested are too insensitive and nonspecific while diagnostics are either too complex or invasive. In Austria, a multicenter study was begun to search for parameters appropriate for a screening program. 138 women were selected based on anamnestic, serologic and cytologic risk factors. 68 women were diagnosed with endometrial cancer, 70 patients had abnormal bleeding. There were no significant differences in age and menopausal status. Secondary diseases including diabetes mellitus, hypertonia and adipositas were evenly distributed in both groups. In addition to the routine hormone analyses, we tested the patients' plasma for differences in melatonin levels. We found a significant correlation ( $p < 0.001$ ) between melatonin plasma levels and the presence of endometrial cancer. The mean plasma melatonin value was 6.1 pg/ml in the cancer-positive group and 33.2 pg/ml in the cancer-negative control group resulting in a 6-fold difference between the two groups. We conclude that decreasing melatonin plasma levels may be an indicator of endometrial cancer and that this may therefore be used as a reliable screening parameter.

**Vitamin supplementation reduces blood homocysteine levels: a controlled trial in patients with venous thrombosis and healthy volunteers.**

den Heijer M, Brouwer IA, Bos GM, et al. *Arterioscler Thromb Vasc Biol* 1998;18:356-361.

Hyperhomocysteinemia is a risk factor for atherosclerosis and thrombosis and is inversely related to plasma folate and vitamin B12 levels. We assessed the effects of vitamin supplementation on plasma homocysteine levels in 89 patients with a history of recurrent venous thrombosis and 227 healthy volunteers. Patients and hyperhomocysteinemic (homocysteine level >16 micromol/L) volunteers were randomized to placebo or high-dose multivitamin supplements containing 5 mg folic acid, 0.4 mg hydroxycobalamin, and 50 mg pyridoxine. A subgroup of volunteers without hyperhomocysteinemia was also randomized into three additional regimens of 5 mg folic acid, 0.5 mg folic acid, or 0.4 mg hydroxycobalamin. Before and after the intervention period, blood samples were taken for measurements of homocysteine, folate, cobalamin, and pyridoxal-5'-phosphate levels. Supplementation with high-dose multivitamin preparations normalized plasma homocysteine levels (< or = 16 micromol/L) in 26 of 30 individuals compared with 7 of 30 in the placebo group. Also in normohomocysteinemic subjects, multivitamin supplementation strongly reduced homocysteine levels (median reduction, 30%; range, -22% to 55%). In this subgroup the effect of folic acid alone was similar to that of multivitamin: median reduction, 26%; range, -2% to 52% for 5 mg folic acid and 25%; range, -54% to 40% for 0.5 mg folic acid. Cobalamin supplementation had only a slight effect on homocysteine lowering (median reduction, 10%; range, -21% to 41%). Our study shows that combined vitamin supplementation reduces homocysteine levels effectively in patients with venous thrombosis and in healthy volunteers, either with or without hyperhomocysteinemia. Even supplementation with 0.5 mg of folic acid led to a substantial reduction of blood homocysteine levels.

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### **Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial.**

Schoenen J, Jacquy J, Lenaerts M. *Neurology* 1998;50:466-470.

A deficit of mitochondrial energy metabolism may play a role in migraine pathogenesis. We found in a previous open study that high-dose riboflavin was effective in migraine prophylaxis. We now compared riboflavin (400 mg) and placebo in 55 patients with migraine in a randomized trial of 3 months duration. Using an intention-to-treat analysis, riboflavin was superior to placebo in reducing attack frequency ( $p = 0.005$ ) and headache days ( $p = 0.012$ ). Regarding the latter, the proportion of patients who improved by at least 50%, i.e. "responders," was 15% for placebo and 59% for riboflavin ( $p = 0.002$ ) and the number-needed-to-treat for effectiveness was 2.3. Three minor adverse events occurred, two in the riboflavin group (diarrhea and polyuria) and one in the placebo group (abdominal cramps). None was serious. Because of its high efficacy, excellent tolerability, and low cost, riboflavin is an interesting option for migraine prophylaxis and a candidate for a comparative trial with an established prophylactic drug.

### **Induction of apoptosis in human stomach cancer cells by green tea catechins.**

Hibasami H, Komiya T, Achiwa Y, et al. *Oncol Rep* 1998;5:527-529.

The exposure of human stomach cancer KATO III cells to green tea catechin extract and epigallocatechin gallate (EGCG), a main component of the extract led to both growth inhibition and the induction of programmed cell death (apoptosis). Morphological changes showing apoptotic body were observed in the cells treated with green tea catechin extract and EGCG. The fragmentation of DNA to oligonucleosomal-sized fragments, characteristic of apoptosis was determined to be concentration- and time-dependent. These data suggest that drinking of green tea in large amounts is recommended possibly to protect humans from stomach cancer.

### **Effect of melatonin on tinnitus.**

Rosenberg SI, Silverstein H,  
Rowan PT, Olds MJ.

*Laryngoscope*

1998;108:305-310.

**OBJECTIVE:** Evaluate melatonin as a treatment for subjective tinnitus. **STUDY DESIGN:** Randomized, prospective, double-blind, placebo-controlled crossover trial. Patients were given 3.0 mg melatonin, which was taken nightly for 30 days followed or preceded by a placebo nightly for 30 days, with a 7-day washout period between medications. **SETTING:** Outpatient, private, neurotology practice. **PATIENTS:** Thirty patients with subjective tinnitus. **MAIN OUTCOME MEASURES:** Tinnitus matching, Tinnitus Handicap Inventory (THI), patient questionnaire and interview. **RESULTS:** The average pretreatment THI score was 33.91 as compared with 26.43 after the placebo and 26.09 after melatonin. The difference in the THI scores between melatonin and placebo treatment were not statistically significant. The average pretreatment THI score for patients who reported overall improvement with melatonin was statistically higher ( $P = 0.02$ ) than the average pretreatment THI score for patients who reported no improvement with melatonin. Among subjects reporting difficulty sleeping attributable to their tinnitus, 46.7% reported an overall improvement after melatonin compared with 20.0% for placebo ( $P = 0.04$ ). There was also a statistically significant difference in improvement with melatonin for those patients with bilateral tinnitus compared with those with unilateral tinnitus ( $P = 0.02$ ). **CONCLUSION:** Melatonin has been shown to be useful in the treatment of subjective tinnitus. Patients with high THI scores and/or difficulty sleeping are most likely to benefit from treatment with melatonin. In light of its minimal side effects, melatonin should be a part of the physician's armamentarium in the treatment of tinnitus.

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### **Nutritional factors that can favorably influence the glucose/insulin system: vanadium.**

Verma S, Cam MC, McNeill JH. *J Am Coll Nutr* 1998;17:11-18.

A growing body of experimental and clinical research indicates that the trace element, vanadium, exerts potent insulin-mimetic effects in vitro and in vivo when used in pharmacological doses. Since our first demonstration of the anti-diabetic and cardioprotective effects of vanadium in vivo, impressive advances have been made in our understanding of its mechanism of action, pharmacokinetics and pharmacodynamics. A major advance in the use of vanadium as an insulin-mimetic has been the development of organic vanadium complexes which are 2 to 3 times as potent as inorganic vanadium and have been extensively studied in our laboratory. There is an emerging role for the use of vanadium in human diabetes and the recently conducted clinical trials support this contention. The present review summarizes some of the key aspects of vanadium biology which exemplify the potent insulin-mimetic, anti-diabetic and antihypertensive effects of this intriguing trace element.

### **Inhibitory action of silibinin on low density lipoprotein oxidation.**

Locher R, Suter PM, Weyhenmeyer R, Vetter W. *Arzneimittelforschung* 1998;48:236-239.

Low density lipoprotein (LDL) oxidation and smooth muscle cell growth represent key events in atherogenesis. Any means to reduce these two phenomena may decrease the risk of coronary artery disease and atherosclerosis in general. The effects of silibinin (CAS 22888-70-6) on LDL oxidation and proliferation of vascular smooth muscle cells were evaluated in vitro. Silibinin (50-200  $\mu\text{mol/l}$ ) prolonged the lag times of both LDL autooxidation and oxidation by copper by > 50%, as assessed by recordings of diene formation. However, silibinin (up to 500  $\mu\text{mol/l}$ ) did not interfere with LDL-stimulated radiolabeled thymidine incorporation. These findings indicate that silibinin, apart from its hepatoprotective effects, has inhibitory properties on LDL oxidation in vitro. Therefore silibinin might represent a novel tool in the prevention and therapy of atherosclerosis.

**Quantitation of chemopreventive synergism between (-)-epigallocatechin-3-gallate and curcumin in normal, premalignant and malignant human oral epithelial cells.**

Khafif A, Schantz SP, Chou TC, et al. *Carcinogenesis* 1998;19:419-424.

An in vitro model for oral cancer was used to examine the growth inhibitory effects of chemopreventive agents when used singly and in combination. The model consists of primary cultures of normal oral epithelial cells, newly established cell lines derived from dysplastic leukoplakia and squamous cell carcinoma. Two naturally occurring substances, (-)-epigallocatechin-3-gallate (EGCG) from green tea and curcumin from the spice turmeric were tested. Cells were treated singly and in combination and effects on growth determined in 5-day growth assays and by cell cycle analysis. Effective dose 50s and the combination index were calculated with the computerized Chou-Talalay method which is based on the median-effect principle. Agents were shown to differ in their inhibitory potency. EGCG was less effective with cell progression; the cancer cells were more resistant than normal or dysplastic cells. In contrast, curcumin was equally effective regardless of the cell type tested. Cell cycle analysis indicated that EGCG blocked cells in G1, whereas curcumin blocked cells in S/G2M. The combination of both agents showed synergistic interactions in growth inhibition and increased sigmoidicity (steepness) of the dose-effect curves, a response that was dose and cell type dependent. Combinations allowed for a dose reduction of 4.4-8.5-fold for EGCG and 2.2-2.8-fold for curcumin at ED50s as indicated by the dose reduction index (DRI). Even greater DRI values were observed above ED50 levels. Our results demonstrate that this model which includes normal, premalignant and malignant oral cells can be used to analyse the relative potential of various chemopreventive agents. Two such naturally-occurring agents, EGCG and curcumin, were noted to inhibit growth by different mechanisms, a factor which may account for their demonstrable interactive synergistic effect.

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**A woman with five consecutive fetal deaths: case report and retrospective analysis of hyperhomocysteinemia prevalence in 100 consecutive women with recurrent miscarriages.**

Quere I, Bellet H, Hoffet M, et al. *Fertil Steril* 1998;69:152-154.

**OBJECTIVE:** To evaluate the medical relevance of hyperhomocysteinemia in women with primary recurrent miscarriages. **DESIGN:** Case report and retrospective cross-sectional study. **SETTING:** Hematology outpatient department of a university hospital. **PATIENT(S):** Case report concerning a woman with five consecutive fetal losses. One hundred consecutive women with primary recurrent unexplained miscarriages (study group) and matched healthy controls (control group) with no antecedent fetal loss. **INTERVENTION(S):** Venous blood sample collection in resting individuals. **MAIN OUTCOME MEASURE(S):** Plasma total homocysteine concentrations, plasma folate concentrations, and DNA analysis for the C677T mutation of the 5,10 methylene tetrahydrofolate reductase gene. Normal threshold homocysteine concentration was obtained from values found in the control group (95th percentile). **RESULT(S):** The case patient was hyperhomocysteinemic, was homozygous for the C677T mutation in the methylene tetrahydrofolate reductase gene, and had plasma folate deficiency. Folic acid and pyridoxine administration normalized the homocysteine concentration and favored a successful pregnancy. In the retrospective study, 12 of 100 patients were hyperhomocysteinemic. Twenty percent had the C677T methylene tetrahydrofolate reductase genotype and 15% had low plasma folate concentrations. The highest values of homocysteine concentration were found in patients with both the C677T genotype and folate deficiency. **CONCLUSION(S):** Hyperhomocysteinemia should be identified in women with recurrent miscarriages because therapeutic normalization might permit a normal birth.

**Anticarcinogenic effect of a flavonoid antioxidant, silymarin, in human breast cancer cells MDA-MB 468: induction of G1 arrest through an increase in Cip1/p21 concomitant with a decrease in kinase activity of cyclin-dependent kinases and associated cyclins.**

Zi X, Feyes DK, Agarwal R.  
*Clin Cancer Res*  
1998;4:1055-1064.

There is an increasing interest in identifying potent cancer preventive and therapeutic agents against breast cancer. Silymarin, a flavonoid antioxidant isolated from milk thistle, exerts exceptionally high to complete anticarcinogenic effects in tumorigenesis models of epithelial origin. In this study, we investigated the anticarcinogenic effect of silymarin and associated molecular mechanisms, using human breast carcinoma cells MDA-MB 468. Silymarin treatment resulted in a significantly high to complete inhibition of both anchorage-dependent and anchorage-independent cell growth in a dose- and time-dependent manner. The inhibitory effects of silymarin on cell growth and proliferation were associated with a G1 arrest in cell cycle progression concomitant with an induction of up to 19-fold in the protein expression of cyclin-dependent kinase (CDK) inhibitor Cip1/p21. Following silymarin treatment of cells, an incremental binding of Cip1/p21 with CDK2 and CDK6 paralleled a significant decrease in CDK2-, CDK6-, cyclin D1-, and cyclin E-associated kinase activity with no change in CDK2 and CDK6 expression but a decrease in G1 cyclins D1 and E. Taken together, these results suggest that silymarin may exert a strong anticarcinogenic effect against breast cancer and that this effect possibly involves an induction of Cip1/p21 by silymarin, which inhibits the threshold kinase activities of CDKs and associated cyclins, leading to a G1 arrest in cell cycle progression.

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**Relationships of serum carotenoids, retinol, alpha-tocopherol and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri (United States).**

Dorgan JF, Sowell A, Swanson CA, et al. *Cancer Causes Control* 1998;9:89-97.

To evaluate relationships of serum carotenoids, alpha-tocopherol, selenium, and retinol with breast cancer prospectively, we conducted a case-control study nested in a cohort from the Breast Cancer Serum Bank in Columbia, Missouri (United States). Women free of cancer donated blood to this bank in 1977-87. During up to 9.5 years of follow-up (median = 2.7 years), 105 cases of histologically confirmed breast cancer were diagnosed. For each case, two women alive and free of cancer at the age of the case's diagnosis and matched on age and date of blood collection were selected as controls. A nonsignificant gradient of decreasing risk of breast cancer with increasing serum beta-cryptoxanthin was apparent for all women. Serum lycopene also was associated inversely with risk, and among women who donated blood at least two years before diagnosis, a significant gradient of decreasing breast cancer risk with increasing lycopene concentration was evident. A marginally significant gradient of decreasing risk with increasing serum lutein/zeaxanthin also was apparent among these women. We did not observe any evidence for protective effects of alpha- and beta-carotene, alpha-tocopherol, retinol, or selenium for breast cancer. Results of this study suggest that the carotenoids beta-cryptoxanthin, lycopene, and lutein/zeaxanthin may protect against breast cancer.

### **Oral glutamine slows down whole body protein breakdown in Duchenne muscular dystrophy.**

Hankard RG, Hammond D, Haymond MW, Darmaun D. *Pediatr Res* 1998;43:222-226.

We determined whether glutamine has a protein anabolic effect in six 8-13-y-old boys with Duchenne muscular dystrophy. Children received a 5-h i.v. infusion of L-[1-13C]leucine and L-[2-15N]glutamine in the postabsorptive state on two consecutive days while drinking: 1) flavored water on one day, and 2) the same drink mixed with L-glutamine (800 micromol x kg<sup>-1</sup> x h<sup>-1</sup>), the other day. Oral glutamine administration was associated with an 8% decrease in leucine release from protein breakdown, from 116 +/- 5 to 107 +/- 6 micromol x kg<sup>-1</sup> h<sup>-1</sup> (p < 0.01), and a 35% decrease in leucine oxidation rate from 23 +/- 2 to 15 +/- 2 micromol x kg<sup>-1</sup> x h<sup>-1</sup> (p < 0.01), resulting in no change in the nonoxidative leucine disposal, an index of protein synthesis. Whole body glutamine exchange in plasma doubled from 321 +/- 22 to 623 +/- 24 micromol x kg<sup>-1</sup> x h<sup>-1</sup>, p < 0.01, but glutamine from protein degradation and glutamine de novo synthesis both decreased (91 +/- 4 versus 84 +/- 5 micromol x kg<sup>-1</sup> x h<sup>-1</sup>, p < 0.01, and 230 +/- 21 versus 163 +/- 25 micromol x kg<sup>-1</sup> x h<sup>-1</sup>, p = 0.02, respectively). These data suggest that acute oral glutamine administration might have a protein-sparing effect in children with Duchenne muscular dystrophy, decreasing estimates of whole body protein degradation and glutamine de novo synthesis, therefore sparing nitrogen precursors.

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### **Glutamine supplementation in cancer patients receiving chemotherapy: a double-blind randomized study.**

Bozzetti F, Biganzoli L, Gavazzi C, et al. *Nutrition* 1997;13:748-751.

The purpose of this study was to evaluate the efficacy of glutamine in preventing doxifluridine-induced diarrhea and the potential impact of glutamine on the tumor growth. We investigated 65 patients with advanced breast cancer receiving doxifluridine in a double-blind randomized fashion: 33 patients took glutamine (30 g/d, divided in 3 doses of 10 g each) for 8 consecutive days (5-12h) during each interval between chemotherapy, which was administered from day 1 to 4. Thirty-two patients took an equal dose of placebo (maltodextrine). The incidence of diarrhea was registered after each cycle of chemotherapy and severity was scored by the National Cancer Institute (NCI), Bethesda, Maryland, classification. The tumor response was evaluated by the World Health Organization (WHO) criteria. A total of 278 and 259 cycles (median 10 cycles), respectively, were delivered in glutamine and placebo groups. There were 34 and 32 episodes of diarrhea in glutamine and placebo groups, with no statistical difference overall, in the severity and duration of tumor growth, there was no difference in the response rate (21% and 28% of complete or partial response, respectively), in median time to response (2 mo), or in median duration of response. In conclusion, glutamine did not prevent the occurrence of the doxifluridine-induced diarrhea and did not have any impact on tumor response to chemotherapy.

### **Estrogen and progestin bioactivity of foods, herbs, and spices.**

Zava DT, Dollbaum CM, Blen M. *Proc Soc Exp Biol Med* 1998;217:369-378.

In this study we report on the content and bioactivity of plant (phyto) estrogens and progestins in various foods, herbs, and spices, before and after human consumption. Over 150 herbs traditionally used by herbalists for treating a variety of health problems were extracted and tested for their relative capacity to compete with estradiol and progesterone binding to intracellular receptors for progesterone (PR) and estradiol (ER) in intact human breast cancer cells. The six highest ER-binding herbs that are commonly consumed were soy, licorice, red clover, thyme, tumeric, hops, and verbena. The six highest PR-binding herbs and spices commonly consumed were oregano, verbena, tumeric, thyme, red clover and damiana. Some of the herbs and spices found to contain high phytoestrogens and phytoprogestins were further tested for bioactivity based on their ability to regulate cell growth rate in ER (+) and ER (-) breast cancer cell lines and to induce or inhibit the synthesis of alkaline phosphatase, an end product of progesterone action, in PR (+) cells. In general, we found that ER-binding herbal extracts were agonists, much like estradiol, whereas PR-binding extracts, were neutral or antagonists. The bioavailability of phytoestrogens and phytoprogestins in vivo were studied by quantitating the ER-binding and PR-binding capacity of saliva following consumption of soy milk, exogenous progesterone, medroxyprogesterone acetate, or wild mexican yam products containing diosgenin. Soy milk caused a dramatic increase in saliva ER-binding components without a concomitant rise in estradiol. Consumption of PR-binding herbs increased the progestin activity of saliva, but there were marked differences in bioactivity. In summary, we have demonstrated that many of the commonly consumed foods, herbs, and spices contain phytoestrogens and phytoprogestins that act as agonists and antagonists in vivo.

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**Folic acid supplementation prevents deficient blood folate levels and hyperhomocysteinemia during longterm, low dose methotrexate therapy for rheumatoid arthritis: implications for cardiovascular disease prevention.**

Morgan SL, Baggott JE, Lee JY, Alarcon GS. *J Rheumatol* 1998;25:441-446.

**OBJECTIVE:** To determine the effect of longterm methotrexate (MTX) therapy and folic acid supplementation on folate nutriture and homocysteine levels in patients with rheumatoid arthritis. **METHODS:** A double blind, placebo controlled trial lasting one year was conducted at one academic medical center. A total of 79 patients taking low dose MTX were followed up to one year. The patients were randomized to receive placebo or 5 or 27.5 mg folic acid supplementation per week. **RESULTS:** Plasma and erythrocyte folate levels and plasma homocysteine levels were determined. The folate nutriture of patients taking low dose MTX declined without folic acid supplementation. Plasma homocysteine levels increased significantly over a one year period in the placebo group. Low folate nutriture and hyperhomocysteinemia occurred with greater frequency in the placebo group than in the folic acid supplemented groups. **CONCLUSION:** For longterm, low dose MTX therapy, there are now at least 3 reasons to consider supplementation with folic acid (a low cost prescription): (1) to prevent MTX toxicity, (2) to prevent or treat folate deficiency, and (3) to prevent hyperhomocysteinemia, considered by many investigators to be a risk factor for cardiovascular disease.

**Vitamins E plus C and interacting conutrients required for optimal health. A critical and constructive review of epidemiology and supplementation data regarding cardiovascular disease and cancer.**

Gey KF. *Biofactors* 1998;7:113-174.

Antioxidants are crucial components of fruit/vegetable rich diets preventing cardiovascular disease (CVD) and cancer: plasma vitamins C, E, carotenoids from diet correlate prevalence of CVD and cancer inversely, low levels predict an increased risk of individuals which is potentiated by combined inadequacy (e.g., vitamins C + E, C + carotene, A + carotene); self-prescribed rectification of vitamins C and E at adequacy of other micronutrients reduce forthcoming CVD, of vitamins A, C, E, carotene and conutrients also cancer; randomized exclusive supplementation of beta-carotene +/- vitamin A or E lack benefits except prostate cancer reduction by vitamin E, and overall cancer reduction by selenium; randomized intervention with synchronous rectification of vitamins A + C + E + B + minerals reduces CVD and counteracts precancerous lesions; high vitamin E supplements reveal potentials in secondary CVD prevention. Plasma values desirable for primary prevention:  $\geq 30$   $\mu\text{mol/l}$  lipid-standardized vitamin E (alpha-tocopherol/cholesterol  $\geq 5.0$   $\mu\text{mol/mmol}$ );  $\geq 50$   $\mu\text{mol/l}$  vitamin C aiming at vitamin C/vitamin E ratio  $> 1.3-1.5$ ;  $\geq 0.4$   $\mu\text{mol/l}$  beta- ( $> 0.5$   $\mu\text{mol/l}$  alpha+ beta-) carotene. CONCLUSIONS: In CVD vitamin E acts as first risk discriminator, vitamin C as second one; optimal health requires synchronously optimized vitamins C + E, A, carotenoids and vegetable conutrients.

**Anticancer neuroimmunomodulation by pineal hormones other than melatonin: preliminary phase II study of the pineal indole 5-methoxytryptophol in association with low-dose IL-2 and melatonin.**

Lissoni P, Fumagalli L, Paolorossi F, et al. *J Biol Regul Homeost Agents* 1997;11:119-122.

Despite several years of experimental observations, the clinical application of the neuroimmunomodulation is still at the beginning. The pineal gland plays a main role in mediating the link between psychoneuroendocrine and immune systems. Melatonin (MLT), which is the main pineal hormone produced during the night, has appeared to amplify IL-2 anticancer activity. Other pineal hormones, however, would have immunomodulatory activity, in particular 5-methoxytryptophol (5-MTT), which is mainly produced during the light phase of the day. Previous clinical studies have shown that low-dose IL-2 plus MLT may have therapeutic efficacy in advanced cancer patients with neoplasms generally resistant to IL-2 alone, with a tumor regression rate generally less than 20% and an acceptable toxicity. The present study was carried out to evaluate the efficacy of low-dose IL-2 in association with both MLT and 5-MTT. The study included 14 untreatable advanced solid tumor patients (lung cancer: 4; gastric cancer: 3; mesothelioma: 2; hepatocarcinoma: 2; pancreatic cancer: 1; melanoma: 1; colon cancer: 1). IL-2 was injected subcutaneously at 3 MIU/day for 6 days/week for 4 weeks, by repeating a second cycle after a 21-day rest period. Both MLT and 5-MTT were given orally at 40 mg/day in the evening and at 1 mg/day at noon. The clinical results, as evaluated by WHO criteria after each cycle, consisted of partial response (PR) in 4/14 (29%) (lung cancer: 2; hepatocarcinoma: 1; mesothelioma: 1), stable disease (SD) in 6 and progressive disease in the last 4 patients. The treatment was extremely well tolerated in all patients, and in particular no fever greater than 38 degrees C occurred. These preliminary results show that the neuroimmunotherapy with low-dose IL-2 plus two pineal hormones, MLT and 5-MTT, is a well tolerated and potentially effective cancer therapy of untreatable advanced solid tumor patients, with results apparently superior with respect to those previously described with IL-2 plus MLT alone.

### **Effect of resistance exercise on free radical production.**

McBride JM, Kraemer WJ, Triplett-McBride T, Sebastianelli W. *Med Sci Sports Exerc* 1998;30:67-72.

The purposes of this investigation were to see whether free radical production changed with high intensity resistance exercise and, secondly, to see whether vitamin E supplementation would have any effect on free radical formation or variables associated with muscle membrane disruption. Twelve recreationally weight-trained males were divided into two groups. The supplement group (S) received 1200 IUs of vitamin E once a day (3 x 400 IU x d[-1]) for a period of 2 wk. The placebo group (P) received cellulose-based placebo pills once a day for the same period of time. Creatine kinase activity was significantly elevated between preexercise and immediately postexercise, 6 h postexercise, and 24 h postexercise for both groups. The placebo group also had a significant increase in creatine kinase activity at 48 h postexercise. There was a significant difference in creatine kinase activity between the groups at 24 h after exercise. Plasma malondialdehyde significantly increased from preexercise levels for the P group at 6 and 24 h postexercise. Plasma malondialdehyde concentrations significantly increased in the S group between preexercise and immediately postexercise levels. This study indicates that high intensity resistance exercise increases free radical production and that vitamin E supplementation may decrease muscle membrane disruption.

### **Vitamin C improves endothelial function of conduit arteries in patients with chronic heart failure.**

Hornig B, Arakawa N, Kohler C, Drexler H.  
*Circulation* 1998;97:363-368.

**BACKGROUND:** Chronic heart failure (CHF) is associated with endothelial dysfunction including impaired endothelium-mediated, flow-dependent dilation (FDD). There is evidence for increased radical formation in CHF, raising the possibility that nitric oxide is inactivated by radicals, thereby impairing endothelial function. To test this hypothesis, we determined the effect of the antioxidant vitamin C on FDD in patients with CHF. **METHODS AND RESULTS:** High-resolution ultrasound and Doppler was used to measure radial artery diameter and blood flow in 15 patients with CHF and 8 healthy volunteers. Vascular effects of vitamin C (25 mg/min IA) and placebo were determined at rest and during reactive hyperemia (causing endothelium-mediated dilation) before and after intra-arterial infusion of N-monomethyl-L-arginine (L-NMMA) to inhibit endothelial synthesis of nitric oxide. Vitamin C restored FDD in patients with heart failure after acute intra-arterial administration (13.2 $\pm$ 1.7% versus 8.2 $\pm$ 1.0%;  $P<.01$ ) and after 4 weeks of oral therapy (11.9 $\pm$ 0.9% versus 8.2 $\pm$ 1.0%;  $P<.05$ ). In particular, the portion of FDD mediated by nitric oxide (ie, inhibited by L-NMMA) was increased after acute as well as after chronic treatment (CHF baseline: 4.2 $\pm$ 0.7%; acute: 9.1 $\pm$ 1.3%; chronic: 7.3 $\pm$ 1.2%; normal subjects: 8.9 $\pm$ 0.8%;  $P<.01$ ). **CONCLUSIONS:** Vitamin C improves FDD in patients with CHF as the result of increased availability of nitric oxide. This observation supports the concept that endothelial dysfunction in patients with CHF is, at least in part, due to accelerated degradation of nitric oxide by radicals.

### **Micronutrients and breast cancer.**

Franceschi S. *Eur J Cancer Prev* 1997;6:535-539.

A large part of the epidemiological debate on diet and breast cancer has been dominated by the issue of whether fat, particularly animal fat, increases risk. Lately, the possible protective effect of various dietary constituents has received more attention. Vitamins C and E, and beta-carotene have antioxidant activity and may thus provide a cellular defence against reactive oxygen species that damage DNA. Dietary fibre may influence oestrogen metabolism. A large case-control study (2,569 breast cancer and 2,588 hospital controls) conducted in six Italian areas between 1991 and 1994 suggested that a diet rich in several micronutrients was associated with significantly lowered risk. After allowance for non-dietary risk correlates, energy intake and the mutual confounding effect of the various micronutrients, beta-carotene, vitamin E and calcium were associated with odds ratios in the highest intake quintile compared to the lowest one of 0.84, 0.75 and 0.81, respectively. Among different types of fibre, only cellulose intake showed a moderate inverse association. Evidence from other studies suggests that a favourable role of some micronutrients is possible, albeit probably less important than for cancers of the stomach and colon-rectum. Indeed, the relationship between fruit and vegetable intake is also less marked/consistent for breast cancer than for other sites. Among agents that have only recently been investigated, isoflavones, which are weak oestrogens, are of particular interest.

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### **Prospective evaluation of vitamin E for hot flashes in breast cancer survivors.**

Barton DL, Loprinzi CL, Quella SK, et al. *J Clin Oncol* 1998;16:495-500.

**PURPOSE:** Hot flashes represent a substantial clinical problem for some breast cancer survivors. Although estrogen or progesterone preparations can alleviate these symptoms in many patients, concern remains regarding the use of hormonal preparations in such women. Thus, there is a perceived need for nonhormonal treatments for hot flashes for breast cancer survivors. Based on anecdotal evidence that vitamin E was helpful, we designed a trial to investigate this matter. **METHODS:** We developed and conducted a placebo-controlled, randomized, crossover trial where, after a 1 week baseline period, patients received 4 weeks of vitamin E 800 IU daily, then 4 weeks of an identical-appearing placebo, or vice versa. Diaries were used to measure potential toxicities and hot flashes during the baseline week and the two subsequent 4-week treatment periods. **RESULTS:** The 120 patients evaluated for toxicity failed to show any. The 105 patients who finished the first treatment period showed a similar reduction in hot flash frequencies (25% v 22%;  $P = .90$ ) for the two study arms. A crossover analysis, however, showed that vitamin E was associated with a minimal decrease in hot flashes (one less hot flash per day than was seen with a placebo) ( $P < \text{or} = .05$ ). At the study end, patients did not prefer vitamin E over the placebo (32% v 29%, respectively). **CONCLUSION:** Although this trial was able to show a statistically significant hot flash reduction with vitamin E compared to a placebo, the clinical magnitude of this reduction was marginal.

**Effect of parenteral medium- and long-chain triglycerides on lymphocytes subpopulations and functions in patients with acquired immunodeficiency syndrome: a prospective study.**

Gelas P, Cotte L, Poitevin-Later F, et al. *JPEN J Parenter Enteral Nutr* 1998;22:67-71.

**BACKGROUND:** Total parenteral nutrition (TPN) may offer significant clinical benefit in malnourished patients with acquired immunodeficiency syndrome (AIDS). However, the immunologic effect of parenteral lipids remains unknown in these severely immunodepressed patients. **METHODS:** We undertook a prospective randomized double-blind multicenter study comparing the effects of two i.v. lipid emulsions used during TPN: long-chain triglycerides (LCT) or balanced emulsion of long-and medium-chain triglycerides (LCT/MCT). Thirty-three AIDS patients requiring TPN for wasting and reduced oral intake were allocated randomly to receive a ternary TPN mixture consisting of 1.5 g/kg/d proteins, 18 kcal/kg/d lipids, and 12 Kcal/kg/d carbohydrates for 6 days. The following tests were performed at days 0 and 7: immunoglobulins, complement fractions, lymphocyte subpopulations count, and lymphocyte proliferation with mitogens. **RESULTS:** Patients were all severely malnourished (weight loss: -14.0 +/- 1.3 kg). No clinical or biological differences were observed between the groups at baseline. At day 7, both groups reported a significant increase in weight. Patients in the LCT group exhibited a significant decrease in phytohemagglutinin A response ( $p = .04$ ) compared with baseline. Patients in the LCT/MCT group exhibited a lower level of IgM ( $p = .03$ ) and significant increase in C3 fraction ( $p = .03$ ) compared with baseline. They also showed a tendency to have a higher CD4/CD8 lymphocyte ratio ( $p = .07$ ), whereas other immunological parameters remained unchanged. **CONCLUSIONS:** Parenteral ternary mixture containing LCT or LCT/MCT are clinically well tolerated in AIDS patients over 6 days. With 2 g/kg/d of lipids, LCT seems to induce significant abnormalities in lymphocyte function. Such abnormalities are not observed with LCT/MCT.