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Soffritti M, Belpoggi F, Esposito DE, et al: First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. Environ Health Perspect. 2006;113:379-385.

Background. Aspartame is a widely used artificial sweetener, with average daily consumption of 2 to 3 mg/kg in the United States. As part of an integrated series of “mega-experiments,” the investigators assessed the carcinogenic effects of lifelong aspartame consumption in rats.

Methods. Starting at age 8 weeks, Sprague-Dawley rats were fed aspartame in concentrations ranging from 0 to 100,000 ppm. Each group included 100 to 150 rats of each sex. Feeding continued until the animals died of natural causes, at which time histopathologic studies were performed.

Results. The percentage of animals with malignant tumors was higher in the aspartame groups. Although increased cancer rates were noted in both males and females, incidence was highest among female animals receiving a 50,000 ppm concentration of aspartame. Trends toward increased rates of lymphomas and leukemias were especially strong in female rats fed at concentrations of 400 ppm or higher. There was also an increased incidence of transitional cell carcinomas and dysplasias of the renal pelvis ureter, again most marked in female animals receiving aspartame. Trends toward increased rates of lymphomas and leukemias were especially strong in female rats fed at concentrations of 400 ppm or higher. There was also an increased incidence of transitional cell carcinomas and dysplasias of the renal pelvis ureter, again most marked in female animals receiving aspartame concentrations of 400 ppm or higher. Evidence of a carcinogenic effect was noted even at an aspartame concentration of 20 mg/kg/d—well below the U.S. and European acceptable daily intake.

Conclusions. This “mega-experiment” shows evidence of multipotential carcinogenic effects of the artificial sweetener aspartame. The results suggest increases in several types of malignancies in aspartame-fed animals, particularly in females receiving higher concentrations. Studies to re-examine the long-term safety of aspartame should be an urgent priority.

Commentary: Hundreds of studies have been done on aspartame. In a recent analysis of 166 scientific articles, all 74 studies sponsored by the aspartame industry concluded that aspartame was safe while 84 of 92 independent studies found adverse health effects. How can this be? One reason could be that industry-sponsored studies often sacrifice animals early, before adverse events would normally be seen. We know that two-thirds of cancers in humans are diagnosed in persons older than 55 years of age. If you shorten animal experiments so as to avoid the development of cancer, you will not see this adverse effect. For a chemical used by hundreds of millions of people around the world, the precautionary principle should apply. Aspartame needs to be shown to be absolutely safe, particularly since there are alternatives.

Fan S, Meng Q, Auborn K, et al: BRCA1 and BRCA2 as molecular targets for phytochemicals indole-3-carbinol and genistein in breast and prostate cancer cells. Br J Cancer. 2006;94:407-426.

Background. Previous studies have suggested that indole-3-carbinol (I3C), derived from cruciferous vegetables, and genistein, derived from soy, may protect against the development of hormone-responsive tumors. Studies in human breast cancer cells have found that I3C induces expression of the breast cancer susceptibility gene BRCA1, while both I3C and BRCA1 block estrogen (E2) receptor-stimulated estrogen receptor (ER-α) activity. Further studies were performed to evaluate the effects of I3C and genistein on BRCA expression in breast and prostate cancer cell lines.

Methods and Results. In both types of cancer cells, both I3C and genistein induced expression of BRCA1 and BRCA2. Gene expression increased with culture time and concentration; expression was induced at concentrations as low as 20 M for I3C and 0.5 to 1.0 M for genistein. In combination, I3C and genistein induced higher than expected levels of BRCA expression.

In additional experiments, induction of BRCA2 appeared to result at least partly from BRCA1, while the cytotoxic effect mediated by I3C was at least partly dependent on both BRCA1. For both phytochemicals, BRCA1 played a role in inhibiting E2-stimulated ER-α activity. BRCA1 small-interfering RNAs partially reversed the inhibition of ligand-inducible androgen receptor activity.

Conclusions. The results add to the evidence that the phytochemicals I3C and genistein may have a preventive effect on breast and prostate cancer. The BRCA genes appear to be important molecular targets for some actions of I3C and genistein. The fact that BRCA expression occurs in response to low concentrations of I3C and/or genistein may have important implications for prevention of hormone-responsive breast cancers.

Commentary: This study shows that cruciferous vegetables (cabbages, broccoli, brussels sprouts, etc.) and soy contain chemicals that appear to enhance DNA repair in cells, which could lead to protection against cancer. Rosen and coworkers showed that I3C, found in broccoli, cauliflower and cabbage, and a chemical called genistein, found in soy beans, can increase levels of BRCA1 and BRCA2. These proteins repair damaged DNA. Many readers may think this is old news; however, the study is one of the first to provide a molecular explanation as to how eating vegetables might reduce the risk of developing cancer. The researchers exposed breast and prostate cancer cells to I3C and genistein, and found that these chemicals boosted production of BRCA1, as well as its sister repair protein, BRCA2. Decreased amounts of BRCA proteins are seen in cancer cells; therefore, higher levels might prevent cancer from developing.

Bent S, Kane C, Shinohara K, et al: Saw palmetto for benign prostatic hyperplasia. N Engl J Med. 2006;354:557-566.

Background. Saw palmetto is widely used as a treatment for benign prostatic hyperplasia (BPH). Its clinical efficacy was evaluated in a randomized, double-blind trial.

Methods. The study included 225 men, aged 50 years or older, with moderate to severe BPH symptoms. They were randomly assigned to receive saw palmetto extract, 160 mg twice daily; or placebo. Treatment continued for 1 year. The main study end-
points were change in the American Urological Association Symptom Index and in maximal urinary flow rate. Other clinical and laboratory outcomes were monitored as well, along with adverse effects.

**Results.** There was little or no difference in outcomes between groups. The mean difference in symptom change score was 0.04 point, while mean difference in maximal urinary flow rate was just 0.43 ml/min. None of the secondary outcomes—including prostate size, postvoiding residual volume, quality of life, and serum prostate-specific antigen—was significantly different with saw palmetto vs placebo.

**Conclusions.** This randomized, controlled trials question the clinical benefits of saw palmetto for older men with BPH. There is no evidence of improvement in symptoms, urodynamic parameters, or laboratory results.

**Commentary:** This study, in contrast to the many that have been published before, revealed no benefit from the use of saw palmetto in prostatic hyperplasia. Since other studies have used not only different extracts of saw palmetto but also saw palmetto in combination with other herbs, the results underscore the need for more research using standardized extracts. A new NIH-funded study comparing saw palmetto, *Pygeum africanum* (an evergreen bark extract), *tamsulosin* (Flomax), and placebo is in the planning stages. *Pygeum africanum* is commonly combined with saw palmetto in commercially available formulas.

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**Chantry CJ, Howard CR, Auinger P: Full breastfeeding duration and associated decrease in respiratory tract infection in US children. Pediatrics. 2006;117:425-432.**

**Background.** Current recommendations state that infants should be breast-fed exclusively for the first 6 months of life. This guideline is based on studies showing a lower rate of gastrointestinal infection with 6 months of exclusive breast-feeding, compared with 4 months. Rates of respiratory tract infection were not significantly different between the two durations. This study sought to determine whether a full 6 months of breast-feeding was necessary to derive the full protective effect against respiratory infections.

**Methods.** The analysis used data on 2,277 children, aged 6 to 24 months, from the National Health and Nutrition Examination Survey III. Rates of respiratory tract infections—including pneumonia, repeated episodes of colds/influenza or otitis media, or wheezing—were compared for children in five different categories of breast-feeding. Infants requiring neonatal ICU admission were excluded.

**Results.** Pneumonia occurred in 1.6% of infants breast-fed exclusively, compared to 6.5% of those breast-fed for at least 4 but less than 6 months. Other outcomes were similar between groups, including the percentage of infants with three or more episodes of cold/influenza or otitis media, wheezing, and first episode of otitis media before age 1. After adjustment for demographic factors, child care, and smoke exposure, infants breast-fed for at least 4 but less than 6 months were at significantly higher risk of pneumonia (odds ratio 4.27) and three or more episodes of otitis media (odds ratio 1.95) than those breast-fed exclusively for 6 months.

**Conclusions.** Based on population-based epidemiologic data, infants who are not breast-fed exclusively for 6 months are at higher risk of certain types of respiratory tract infections. Shorter durations of breast-feeding—even for more than 4 but less than 6 months—are associated with increased rates of pneumonia and recurrent otitis media. For full health benefits, infants should receive breast milk only for the first 6 months of life, if possible.

**Commentary:** Most of our readers will probably assume this is old news. However, it is important to remember that as recently as 2005, the American Association of Pediatricians’ Committee on Nutrition said more research was needed to support the recommendation for 6 months of exclusive breast-feeding. It is hoped that studies such as this will put the doubts to rest. The evidence continues to show that the longer a mother breast-feeds her infant, the greater the health benefits and protection against a variety of ailments. Despite this evidence, the reality for many nursing women is that breast-feeding is difficult, particularly after going back to work. We hope that research like this will help the situation.

**Garrow D, Egede LF: Association between complementary and alternative medicine use, preventive care practices, and use of conventional medical services among adults with diabetes. Diab Care. 2006;29:15-19.**

**Background.** Previous studies have suggested that use of complementary and alternative medicine (CAM) therapies may be a barrier to conventional medical care for diabetes. A large sample of diabetic patients were surveyed regarding their use of CAM, including its impact on use of conventional medical services and compliance with preventive care.

**Methods.** Nearly 2,500 adult patients with diabetes were surveyed regarding the use of any type of CAM therapy, such as diets and herbal supplements, chiropractic, yoga, relaxation, acupuncture, and others. Logistic regression analysis was performed to assess the relationship between CAM use and specific types of preventive care, ie, influenza and pneumonia vaccination; and conventional medical services, ie, primary care and emergency department visits.

**Results.** Forty-eight percent of diabetic patients reported using some type of CAM therapy. Patients using CAM were more likely to receive pneumonia vaccine, adjusted odds ratio (OR) 1.56, although not influenza vaccine. Use of CAM was also independently associated with use of conventional medical services, including emergency department visits (OR 1.34) and primary care visits (OR 1.44 for six or more visits and 1.66 for eight or more visits).

**Conclusions.** For adult patients with diabetes, use of CAM therapies seems to be associated with increased use of conventional medical care. In this large survey, CAM users are actually more likely to practice preventive care and to make emergency department and primary care visits.

**Commentary:** This study is line with the research evidence suggesting that CAM is often used in conjunction with rather than instead of conventional care. The results underscore the need for conventional physicians to query their patients about all medical therapies they may be using.
Engelhard YN, Gazer B, Paran E: Natural antioxidants from tomato extract reduce blood pressure in patients with grade-1 hypertension: a double-blind, placebo-controlled pilot study. Am Heart J. 2006;151:100.e6-100.e1.

Background. Nutrition plays an important role in the prevention and treatment of primary hypertension. Previous studies have demonstrated the presence of various natural carotenoids in tomato extract, which act as effective antioxidants. This pilot study evaluated the effects of tomato extract on blood pressures and laboratory markers in patients with grade 1 hypertension.

Methods. The single-blind trial included 31 primary care patients with grade 1 hypertension, defined as a blood pressure of 140 to 159/90 to 99 mm Hg. All patients were free of other diseases and were not taking any antihypertensive or lipid-lowering drug therapy. All received 8 weeks of treatment with tomato extract, in the form of Lyc-O-Mato 250 mg. This supplement contained 15 mg of lycopene, along with beta carotene, phytone, phytoflavone, vitamin E, phospholipids, and phytosterol. Patients also received 4 weeks of placebo, before and after the active treatment period.

Results. Tomato extract treatment was associated with a significant reduction in blood pressure: from 144/87.4 to 134/83.4 mm Hg. There was no change in blood pressure during placebo treatment. Laboratory studies showed a significant decrease in thiobarbituric acid-reactive substances, which reflect lipid peroxidation products. Lipid profile was unaffected by the use of tomato extract.

Conclusions. The tomato extract used in this study reduces blood pressure in treatment-naive patients with grade 1 hypertension. The long-term benefits of treatment, including its influence on other cardiovascular risk factors, remain to be determined.

Commentary: The dietary supplement lycopene, derived from tomatoes, may help in treating mild hypertension. Researchers in Israel, using Lyc-O-Mato®, found that a daily dose of tomato extract helped lower blood pressure in 31 men and women with moderately elevated blood pressure. On average, their systolic pressure dropped 10 points while their diastolic pressure, dropped 4 points. Other studies suggest that lycopene, which is an antioxidant, may also reduce the risk of heart disease.

Matsuzaki T, Nakajima A, Ishigami S, et al: Mirthful laughter differentially affects serum pro- and anti-inflammatory cytokine levels depending on the level of disease activity in patients with rheumatoid arthritis. Rheumatology. 2006;45:182-186.

Background. Laughter has been suggested to have positive health effects. This study examined the effects of "mirthful laughter" on serum cytokine levels in patients with rheumatoid arthritis (RA) and differing levels of disease activity.

Methods. Mirthful laughter was induced in 41 RA patients and 23 controls by having them listen to a traditional Japanese comic story. Serum cytokine levels were measured before and after the story. Cytokine effects were compared for patients with "difficult-to-control" vs "easily controlled" RA, based on C-reactive protein level.

Results. At baseline, interleukin (IL)-6 and tumor necrosis factor-α levels were higher in the RA patients than in the healthy controls. Mirthful laughter was associated with significant reductions in IL-6 in the RA patients, but not in controls. Serum IL-4 was also higher than normal in RA patients at baseline and decreased after mirthful laughter, particularly in the patients with "difficult-to-control" RA. Serum IL-1 receptor antagonist was higher in RA patients than in controls at baseline, and increased further after the story. The increase in IL-1 receptor antagonist was more pronounced among patients with "easily controlled" RA.

Conclusions. Mirthful laughter is associated with changes in cytokine levels in patients with RA. The pattern of change in proinflammatory vs anti-inflammatory cytokines varies for RA patients at differing levels of disease control.

Commentary: This study demonstrates that laughter—often recognized as good medicine—may help difficult to control RA. This study underscores the importance of addressing not only the physical but also the psychologic stresses of RA. These researchers evaluated the effect of laughter on proinflammatory and anti-inflammatory cytokines. They found that, after laughter, the levels of serum IL-6 decreased significantly in the group of patients with RA. These results suggest that immunologic and psychologic processes both regulate the body’s response in RA and play a role in the progression of autoimmune diseases.

Milazzo S, Russell N, Ernst E: Efficacy of homeopathic therapy in cancer treatment. Eur J Cancer. 2006;282-289.

Background. Particularly in Europe, many patients with cancer use homeopathy to increase strength, enhance well-being, and reduce pain. The absence of a "plausible" mechanism of action has raised doubts about the efficacy of homeopathic treatments. The authors performed a systematic review of the literature on homeopathic treatments used in cancer care.

Methods. A literature search was performed to identify randomized or nonrandomized controlled trials of homeopathic treatments used by patients with current or previous cancer. Methodologic quality was rated using the Jadad score. The clinical evidence for the effectiveness of any type of homeopathic remedy in cancer care was critically evaluated.

Results. The review identified six studies: five randomized and one nonrandomized trial. Sample size ranged from 27 to 82. Quality was variable, although four of the studies had Jadad scores of 4 or 5. The studies investigated a wide range of homeopathic treatments, singly or in combination, used for many different indications. In some studies, patients received individualized homeopathic therapy.

Five of the six studies reported positive effects of homeopathic treatments, particularly for the indications of chemotherapy-induced stomatitis, radiodermatitis, and overall side effects of radiation therapy. One trial showed improved quality of life in women with a history of breast cancer who were experiencing menopausal symptoms. However, only two studies reported statistically significant improvements in their primary outcomes.

Conclusions. A systematic review of the literature on homeopathic treatments in cancer care finds insufficient data on efficacy. Some positive effects are reported, particularly on adverse effects of chemotherapy and radiation therapy. Other studies...
Many questions remain about the nature and existence of the placebo effect. It has been suggested that placebo devices have stronger effects than placebo pills; the informed consent process may also influence the placebo effect. This trial compared the effects of a sham acupuncture intervention and an oral placebo pill.

Methods. The study included 270 patients evaluated for distal arm pain related to repetitive motion or overuse. All had pain rated 3 or higher on a 10-point scale that had been present for at least 3 months. The study analyzed data from the 2-week placebo run-in periods of two placebo-controlled trials of acupuncture and amitriptyline. The two placebo interventions were compared: a validated sham acupuncture intervention and an inert oral pill. After the run-in period, patients were re-randomized to receive continued placebo or active treatment of the same type: two acupuncture treatments per week for an additional 4 weeks or oral pill treatment for an additional six weeks.

Results. Arm pain decreased to a similar extent during the 2-week run-in period in both placebo groups. Patients taking the placebo pill had a greater improvement in arm function, but there was no difference on a symptom severity scale or a grip strength test. On continued follow-up to the end of the study, the downward slope in arm pain was greater with sham acupuncture than with placebo pill: −0.33 vs 0.15 per week. There was a similar difference on the symptom severity scale. Adverse effects were completely different between groups, reflecting the information provided at informed consent.

Conclusions. This study finds significant differences in the response to placebo device vs pill in patients with arm pain. Sham acupuncture yields greater reductions in arm pain and symptom severity across the entire course of treatment, although not during an initial run-in period. The findings suggest that placebo effects can be detected beyond the natural evolution of disease, and that adverse effects vary with the information given to patients.

Commentary. This article by Kaptchuk et al. provides another fascinating chapter on the complex role of placebos. The trial, funded by the National Institutes of Health, pitted one placebo against another and investigated whether a sham acupuncture device had a greater placebo effect than an inert pill in 270 individuals with chronic arm pain. In the first part, 135 patients were given sham acupuncture and 135 were given a placebo pill. In the second part of the study, the patients were randomized, with half the patients entered into a sham acupuncture device trial compared with real acupuncture, and the other half in a placebo pill vs real pain pill trial. The acupuncture trial extended 4 more weeks and the pill trial lasted 6 more weeks. The results show that the placebo effect varies by the type of placebo used—suggesting that the medical ritual of using a device (from acupuncture, in this case, to surgery) can deliver an enhanced placebo effect beyond that of a placebo pill. In some cases, the ritual may be the critical therapeutic intervention. These results suggest that what doctors tell patients may directly influence their experience of what is done. Before the study, doctors alerted patients about the side effects they might experience with active and placebo treatment—25% reported side effects even with placebo. The use of placebos in clinical trials assumes a standardization and linearity of the placebo response. However, not only has this never been demonstrated to be true, but there is a growing body of evidence suggesting otherwise.

Puhan M, Suarez A, Cascio C, et al: Didgeridoo playing as alternative treatment for obstructive sleep apnoea syndrome: randomised controlled trial. BMJ. 2006;332:266-270.

Background. Continuous positive airway pressure is the treatment of choice for patients with obstructive sleep apnoea syndrome (OSAS). It would be helpful to have other treatments to improve symptoms such as snoring and daytime sleepiness in less severely affected patients. Training in playing a musical instrument, the didgeridoo, was evaluated as a possible alternative treatment for OSAS.

Methods. The randomized, controlled trial included 25 patients with moderate OSAS. All had an apnea-hypopnea index of 15 to 30, together with symptoms of snoring. One group of patients received didgeridoo lessons, including instruction in the “circular breathing” technique needed to play the instrument. Patients were to practice daily at home. Controls were assigned to a waiting list. Daytime sleepiness, apnea-hypopnea index, and other outcomes were compared.

Results. Patients in the intervention group practiced for an average of 25 minutes per day, 6 days per week. Daytime sleepiness improved significantly in the didgeridoo group, with a between group difference of 3.0 on the Epworth scale. Didgeridoo playing was also associated with a 6.2-point difference in apnea-hypopnea index. Partners of patients in the didgeridoo group reported reduced sleep disturbance; there was no difference in sleep quality or health-related quality of life between groups.

Conclusions. Didgeridoo playing can improve objective disease severity and daytime sleepiness in patients with moderate OSAS. Didgeridoo training and practice are well tolerated by patients and have a moderate to large effect on sleep outcomes.

Commentary. Didgeridoo playing—which involves training of the respiratory system to even use the instrument—appears to be an effective treatment for patients with moderate OSAS. As intriguing as these results are, I doubt that patients across this country are going to begin playing the didgeridoo. However, they may begin to do breathing exercises that could also modify their OSAS.
Liu X, Zhang M, He L, et al: Chinese herbs combined with Western medicine for severe acute respiratory syndrome (SARS). Cochrane Database of Systematic Reviews. 2006;Issue 1, Art No: CD004882. DOI: 10.1002/14651858.CD004882.pub2.

Background. Some reports of the initial outbreak of severe acute respiratory syndrome (SARS) in China suggested that Chinese herbal therapy was beneficial. This systematic review evaluated research on the effectiveness of Chinese herbs, added to Western therapies, for the treatment of SARS.

Methods. The investigators searched the literature, including the Chinese literature, for randomized and quasi-randomized studies of Chinese herbal therapy for SARS. Outcomes were compared for patients receiving Chinese herbs plus Western medicine vs those receiving Western medicine only.

Results. The review identified 12 randomized and 1 quasi-randomized trials. The studies, including a total of 654 patients with SARS, evaluated the effects of 12 different Chinese herbs. Overall, the combination of Chinese herbs with Western medicine did not reduce SARS morbidity, compared with Western medicine alone. Two of the herbs studied were effective in reducing symptoms, while five showed evidence of improved absorption of pulmonary infiltrates. Four herbs were associated with reductions in corticosteroid dosage and three with quality-of-life improvements. Just two studies included information on adverse events.

Conclusions. Adding Chinese herbs to Western medicine does not reduce morbidity in patients being treated for SARS, compared to Western medicine alone. However, some herbs may bring meaningful clinical improvements, including reduced symptoms, improved quality of life, and reduced corticosteroid requirements. Higher-quality studies with longer follow-up are needed to determine the true benefits of Chinese herbal therapy in this form of acute lung disease.

Commentary: A recently identified coronavirus is responsible for SARS, which was first reported in China in 2002. This study was unable to identify any individual Chinese herbs that, when combined with Western medicines, significantly improved the symptoms associated with SARS. However, in some patients treated with Chinese herbs along with Western medicine, fever, cough and breathing difficulty lasted a shorter length of time. One limitation of this review was the poor quality of the trials.

MacLean CH, Newberry SJ, Mojica WA, et al: Effects of omega-3 fatty acids on cancer risk: a systematic review. JAMA. 2006;295:403-415.

Background. Previous studies of the effects of omega-3 fatty acids on cancer risk have yielded conflicting results. Available data on the relationship between omega-3 fatty acid intake and the incidence of cancer were analyzed in a systematic review.

Methods. A literature search was performed to identify prospective cohort studies of the effects of omega-3 fatty acids on cancer risk. Unpublished as well as published studies were sought.

Results. Thirty-eight papers comparing tumor incidence in groups with differing levels of omega-3 fatty acid consumption were identified. The studies—providing data on 11 different cancers in 20 patient cohorts from seven countries—followed six different approaches to measuring omega-3 fatty acid consumption. Of a total of 65 estimates reported, just 8 were statistically significant.

Of 11 studies reporting on the relationship between omega-3 fatty acids and breast cancer, 7 found no significant association, 3 suggested decreased risk, while 1 reported increased risk. One study found a decreased risk of colorectal cancer, but 17 more showed no association. Most studies of lung cancer and prostate cancer also showed no significant association, while a single study of cancer risk suggested an increased risk. None of the other cancers studied were significantly affected by omega-3 fatty acid consumption, including aerodigestive, bladder, ovarian, pancreatic, or stomach cancers and lymphoma.

Conclusions. A substantial body of research evidence has shown little or no consistent relationship between omega-3 fatty acid intake and cancer risk. Omega-3 fatty acid supplements cannot be recommended for cancer prevention.

Commentary: This well-done systematic review of clinical studies did not find strong evidence that the consumption of omega-3 fatty acids reduces the risk of cancer. Epidemiologic studies have suggested that those who consume diets high in omega-3 fatty acids—found in many fish and vegetables—may experience a lower prevalence of some types of cancer. Many smaller trials assessed the effects of omega-3 fatty acids on cancer treatment—in the form of omega-3 fatty acid–rich foods or dietary supplements—with mixed results. These researchers identified 38 articles and found no trend to suggest that omega-3 fatty acids reduce overall cancer risk.

Hilton M, Stuart E: Ginkgo biloba for tinnitus. The Cochrane Database of Systematic Reviews. 2004;Issue 2, Art No: CD003852. DOI: 10.1002/14651858.CD003852.pub2.

Background. Tinnitus is a troublesome problem for which there is no specific, effective therapy. Some studies have suggested that Ginkgo biloba may be helpful, although tinnitus treatment is subject to a strong placebo effect. Research data on the effectiveness of ginkgo biloba for tinnitus were reviewed.

Methods and Results. A literature search was performed to identify trials evaluating Ginkgo biloba for the treatment of tinnitus, as a primary complaint or as part of a complaint of cerebral insufficiency. Of 12 trials identified, 10 were excluded because of methodologic issues, including all trials involving patients with cerebral insufficiency. There was no evidence that Ginkgo was effective for the primary complaint of tinnitus. Few problems with side effects were reported.

Conclusions. Studies to date provide no evidence for the effectiveness of Ginkgo biloba in the treatment of tinnitus. The quality of research on this issue is poor.

Commentary: People with tinnitus bear sounds in the absence of external noise. Ginkgo has been used to treat this and other neurologic conditions. Of the 12 trials identified in this review, none was sufficiently rigorous to draw definitive conclusions. There is therefore no convincing evidence that Ginkgo biloba is effective for tinnitus.
Methods. The literature was reviewed for randomized controlled trials comparing Echinacea with placebo, no treatment, or other treatments for the common cold. Studies assessing combinations of Echinacea with other herbal products were excluded. For treatment trials, outcomes of interest included symptom scores, nasal symptoms, and duration of illness. For prevention studies, the number of affected patients and the severity and duration of colds were assessed.

Results. The 16 trials identified included 22 comparisons, mainly of Echinacea vs placebo. Nearly all were double-blind trials; methodologic quality was rated “reasonable to good” in most cases. There were 19 treatment comparisons and 3 prevention comparisons. A number of different Echinacea preparations were evaluated; the only type of product evaluated by more than one study was preparations using the aerial parts of Echinacea purpurea.

None of the three prevention trials found a significant benefit of Echinacea over placebo. Nine treatment comparisons reported a significant effect of Echinacea compared with placebo, while another showed a trend. The remaining 6 studies found no difference.

Conclusions. Several studies have found Echinacea products effective in treatment, although not in prevention, of the common cold. However, inconsistencies remain even for the best-studied type of Echinacea preparation. Although other types of preparations might be clinically effective, this has yet to be demonstrated in independent, methodologically sound randomized trials.

Commentary: A variety of preparations of the plant Echinacea are used in Europe and North America for treating common colds, as well as for providing a vague sense of immune support. The available preparations vary widely, which confounds clinical research. In this review, 16 controlled clinical trials investigating the effectiveness of several different Echinacea preparations for preventing and treating common colds were evaluated. It appears that some preparations based on the E. purpurea herb might be effective for this purpose in adults, even though overall, no convincing effect was noted.

Schroeter H, Heiss C, Balzer J, et al: (−)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans. Proc Natl Acad Sci USA. 2006;103:1024-1029.

Background. Distinct lines of evidence suggest that foods rich in flavanol, including cocoa, have cardiovascular health benefits. In vitro studies have been performed to assess the possible molecular mechanisms of this effect, but little is known about the bioactivity of specific flavanol metabolites. A series of experiments were performed to evaluate the possible vasoactive effects of dietary flavanols and their metabolites.

Methods and Results. The experiments were designed to address five specific criteria demonstrating that flavanols are mediators of vascular function. In healthy men, consumption of a high-flavanol cocoa drink was followed by an acute rise in circulating nitric oxide (NO) species, increased arterial flow-mediated dilation, and microcirculatory increases. On analysis of circulating flavanoids, (−)-epicatechin and its metabolite epicatechin-7-O-gluconide were independent predictors of the changes in vascular function occurring after consumption of the high-flavanol cocoa drink.

In an ex vivo experiment, preconstricted rabbit aortic rings showed a significant relaxation response—similar to that produced by acetylcholine—in the presence of a combination of flavanols/metabolites designed to mimic the circulating plasma flavanoid profile produced by cocoa ingestion. In humans, treatment with an NO synthase inhibitor attenuated the vascular relaxation and flow-mediated dilation effects of flavanol. Treatment with chemically pure (−)-epicatechin induced responses very similar to those produced by flavanol-rich cocoa. Studies in two groups of Kuna Indians suggested that chronic consumption of a diet high in cocoa flavanols was associated with increased urinary excretion of NO metabolites, consistent with a prolonged state of augmented NO synthesis.

Conclusions. These experimental results help to explain the cardiovascular benefits of flavanol-rich foods such as cocoa. The data support a causal association between a specific cocoa flavanol, (−)-epicatechin, and the vascular effects observed after drinking flavanol-rich cocoa. The findings may aid in developing new dietary or therapeutic approaches to improving cardiovascular health, and in understanding the mechanisms by which diets rich in plant foods reduce the risk of vascular disease.

Commentary: This study, involving the Kuna Indians of Panama who live on the San Blas islands off the coast of Panama, has identified a chemical compound that may be responsible for the heart-healthy benefits of chocolate. High blood pressure is rare among the island-dwelling Kuna, who are also known to consume large amounts of flavanol-rich cocoa—3 to 4 cups per day. Earlier studies found that Kuna who had moved away from San Blas consumed only 4 cups of cocoa per week and did not enjoy the same level of cardiovascular health. By analyzing urine samples from both groups of Indians, the researchers found that, the urine of island Indians had more than twice the levels of NO—a compound associated with healthy flow of blood through the arteries.

In another experiment, levels of NO in the blood were higher in individuals who drank flavanol-rich cocoa, compared to those who drank cocoa beverages with low flavanol levels. Higher levels of the flavanol epicatechin in the bloodstream were accompanied by improved blood flow. Epicatechin, one of the flavanols found in chocolate, was linked to improved circulation and other hallmarks of cardiovascular health.
gested a treatment effect on non-small-cell lung cancers. Two murine models of lung cancer were used to evaluate the possible chemopreventive effects of bexarotene.

**Methods.** Experiments were performed in mutant A/J mice with alterations in genes linked to lung tumor development in humans: p53 or K-ras. At age 6 weeks, the mice underwent intraperitoneal injection of a carcinogenic substance, vinyl carbamate. Sixteen weeks later, the animals began 12 weeks of treatment with bexarotene, administered by gavage. Lung tumor development was assessed in the two groups of genetically altered mice, compared with wild-type mice.

**Results.** Lung tumors developed in all three groups of animals. However, these tumors were significantly more likely to be adenocarcinomas in the genetically altered mice: 22% in p53 transgenic mice and 26% in K-ras heterozygous deficient mice, compared with just 7% in wild-type mice. Across groups, bexarotene was associated with reduced tumor multiplicity and tumor volume. Bexarotene also reduced the likelihood of adenomas progressing to adenocarcinomas by about one-half.

**Conclusions.** Bexarotene prevents the development and progression of lung tumors in animal models. This vitamin A analog may become a valuable chemopreventive agent.

**Commentary:** Bexarotene, a vitamin A analog, appears to help prevent lung cancer by blocking tumor growth without the unpleasant or dangerous side effects that limited the use of vitamin A derivatives in cancer treatment. Bexarotene has also extended survival in patients with non-small-cell lung cancer. In this study, the authors demonstrated that lung-cancer-susceptible mice receiving nontoxic doses of bexarotene ended up with fewer cancers. Retinoids, a new class of vitamin A analogs, appear to be less toxic than retinoids; bexarotene has shown the most promise as a chemopreventive medicine.

Garland CF, Garland FC, Gorham ED, et al: The role of vitamin D in cancer prevention. Am J Pub Health. 2006;96:252-261.

**Background.** Vitamin D levels vary by race and by the latitude at which populations live. Vitamin A deficiency is more common among people in the northeastern United States and those with greater skin pigmentation. This literature review evaluated evidence on the relationship between vitamin D status and cancer risk.

**Methods and Results.** The literature search identified 63 observational studies of the association between vitamin D status and cancer risk. The studies addressed several different types of cancer: colon cancer in 30 studies, prostate cancer in 26, breast cancer in 13, and ovarian cancer in 7. Several studies examined the effects of vitamin D receptor genotype on cancer risk. In most reports, adequate vitamin D status was associated with a lower risk of cancer.

**Conclusions.** Research evidence is consistent with a protective effect of vitamin D status against cancer. Vitamin D supplementation might offer an effective, safe, and low-cost approach to cancer prevention.

**Commentary:** A review of vitamin D research suggests that a daily dose of 1,000 IU of vitamin D can reduce the incidence and mortality associated with colon, breast, prostate, and ovarian cancer. This review searched PubMed in 2004 for epidemiologic studies looking at the association between cancer and vitamin D, sunlight, ultraviolet radiation, and latitude. Most studies found that a sufficient intake of vitamin D protected against cancer, suggesting that improving vitamin D status could reduce cancer incidence.

Wood CE, Register TC, Franke AA, et al: Dietary soy isoflavones inhibit estrogen effects in the postmenopausal breast. Cancer Res. 2006;66:1241-1249.

**Background.** Previous studies have suggested a possible role of soy isoflavones in breast cancer prevention. Acting to bind estrogen receptors (ERs), isoflavones may function as estrogen agonists or antagonists, depending on the estrogen milieu. A primate model of menopause was used to assess the interactions between soy isoflavones and estrogen in influencing markers of breast cancer risk.

**Methods.** Menopause was induced by oophorectomy in mature female cynomolgus monkeys, who were then studied while consuming diets containing various levels of soy isoflavones. Human equivalent soy isoflavone levels ranged from 0 to 240 mg/d. At each level, the monkeys also received 0.09 or 0.5 mg/d doses of oral micronized 17β-estradiol (E2), producing a very low estrogen environment. Each diet/estrogen period continued for 4 months, with a 1-month washout period between diets. Markers of breast cancer risk were compared under each study condition.

**Results.** While receiving the 240 mg/d isoflavone dose in the high-estrogen environment, the animals showed significant reductions in breast proliferation and uterine size. The highest isoflavone dose was also associated with apparently conflicting alterations in breast indicators of ER activation: expression of pS2 was significantly decreased, while expression of progesterone receptor expression was significantly increased. At the high estrogen dose, all doses of isoflavone were associated with reduced serum levels of estrone and E2. At the low estrogen dose, isoflavones produced no estrogen-agonist effects and few estrogen-antagonist effects.

**Conclusions.** In a high-estrogen postmenopausal environment, a diet high in soy isoflavones may produce significant changes in ER signaling. This situation may also be associated with selective estrogen-agonist effects in the postmenopausal primate breast. The patient’s estrogen level may therefore influence the ability of soy isoflavones to prevent breast cancer.

**Commentary:** This trial in monkeys suggests that the natural plant estrogens found in soy do not increase markers of breast cancer risk in postmenopausal (not perimenopausal) women, and in fact may be preventive. Some evidence has suggested that women who consume diets high in soy have lower rates of breast cancer, and that isoflavones may protect against estrogen produced by the body—a risk factor for breast cancer in postmenopausal women. Confounding this evidence, soy isoflavones have also been shown to stimulate breast cancer cells in mice and in cells grown in the laboratory. The authors evaluated the effects of dietary isoflavones in the presence of different levels of estrogen. The four daily isoflavone doses were roughly equivalent to the following human levels: no isoflavones, 60 mg (typical Asian diet), 120 mg (high levels through diet alone), or 240 mg (using isoflavone supplements). In the low-estrogen environment comparable to an Asian diet, no evidence of increased proliferation was seen. These researchers concluded that post-

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menopausal women with higher levels of estrogen may derive the greatest benefit from soy.

Flöistrup H, Swartz J, Bergström A, et al: Allergic disease and sensitization in Steiner school children. J Allergy Clin Immunol. 2006;117:59-66.

Background. The anthroposophic lifestyle has several characteristics that could influence the development of allergic disease, including the use of antibiotics, antipyretics, and vaccines. A previous report noted a reduced atopic rate among children attending Steiner schools, who commonly come from anthroposophic families. However, the specific factors associated with reduced allergy risk remained unclear. A large, international study of Steiner school children was performed to analyze specific protective factors.

Methods. The cross-sectional study included 4,606 children, aged 5 to 13 years, enrolled at Steiner schools in five European countries. Two thousand twenty-four children from non-Steiner schools served as controls. A parental questionnaire was used to collect information on environmental exposures, history of infections, diet, contact with animals, anthroposophic lifestyle, and allergic disease symptoms and allergic diseases. Allergic sensitization was evaluated by blood tests.

Results. Several allergic disease outcomes were less frequent in the Steiner school children, including rhinoconjunctivitis, atopic eczema, and atopic sensitization. Children exposed to antibiotics during the first year of life had higher rates of physician-diagnosed rhinoconjunctivitis, odds ratio (OR) 1.97; asthma, OR 2.79; and atopic eczema, OR 1.63. Early use of fever-reducing drugs was associated with increased rates of asthma and atopic eczema: OR 1.54 and 1.32, respectively. Rhinovirus risk was increased for children who had received measles, mumps, and rubella vaccine, while the rate of IgE-mediated eczema was reduced for children with a history of measles infection.

Conclusion. Several allergic disease outcomes appear to be reduced among children attending Steiner schools. These effects may be related to specific features of the anthroposophic lifestyle, including the limited use of antibiotics and antipyretic drugs. Future studies should address other features of the anthroposophic lifestyle.

Commentary: An anthroposophic lifestyle—excluding use of fewer antibiotics and antipyretics—appears to reduce the risk of allergic disease in children. This study followed more than 6,000 children from five European countries, aged 5 to 13. The results showed that children in Steiner schools (Waldorf schools in the United States) had a lower risk of allergy. Anthroposophic medicine and the anthroposophic lifestyle, developed by Rudolf Steiner, emphasize that health is a combination of mind, body, and spiritual balance. The study compared Steiner school children with their public school counterparts living in the same region. The Steiner school children had a decreased prevalence of current symptoms as well as diagnoses of upper respiratory tract allergies, atopic eczema, and asthma. Early use of antibiotics and fever reducers, along with measles, mumps, and rubella vaccination, were also associated with increased risks of several allergic symptoms and doctor's diagnoses.

Wayne P, Krebs D, Macklin E, et al: Acupuncture for upper-extremity rehabilitation in chronic stroke: a randomized sham-controlled study. Arch Phys Med Rehabil. 2005;86:2248-2255.

Background. In China, acupuncture is commonly used in the treatment of stroke and other neurologic diseases. Although acupuncture is considered a potentially useful adjunctive technique for stroke rehabilitation under current guidelines, research shortcomings limit the ability to make stronger recommendations. This randomized, sham-controlled trial evaluated the benefits of traditional Chinese acupuncture for patients with chronic hemiparesis after stroke.

Methods. The study included 33 poststroke patients with chronic hemiparesis receiving treatment in a hospital stroke rehabilitation program. All had moderate to severe impairment of upper extremity function; time since stroke ranged from less than 1 year to 24 years. Patients were randomly assigned to undergo active acupuncture, individualized according to traditional Chinese medicine diagnoses; or a sham acupuncture intervention. Patients received up to 20 sessions of their assigned treatment sessions, delivered by experienced acupuncturists. Measures of upper extremity function were assessed, along with activities of daily living, quality of life, and mood.

Results. On intention-to-treat analysis, outcomes were similar for patients assigned to traditional Chinese acupuncture vs sham acupuncture. Some significant benefits of active acupuncture were noted among patients who complied with their assigned treatment, including reduced wrist spasticity and increased wrist and shoulder range of motion. There were also trends toward improvement in upper extremity motor function and finger range of motion.

Conclusions. This small, sham-controlled trial finds no significant benefit of traditional Chinese acupuncture for poststroke hemiparesis in intention-to-treat analyses. However, some benefits of active acupuncture were observed among patients who complied with their assigned treatment. The results warrant a larger randomized trial evaluating the use of traditional Chinese acupuncture for patients with chronic stroke symptoms.

Commentary: Acupuncture may be a useful adjunctive therapy in patients who have had strokes, even though there were no statistically significant differences in outcomes between the active and sham acupuncture groups in this study. In some schools of Chinese medicine, a patient's ability to respond to acupuncture is also tied to the length of time since the stroke. Further research is indicated.