

## ABSTRACTS

### Cernitin

#### **Lower urinary tract symptoms and benign prostatic hyperplasia.**

Benign prostatic hyperplasia (BPH) is an important cause of lower urinary tract symptoms (LUTS). However, many other causes, including smooth muscle dysfunction and neurological factors may contribute to these symptoms, and accurate diagnosis is imperative before invasive treatments are chosen. Careful recording of symptoms, giving emphasis on how they interfere with the patient's quality of life, as well as the use of properly selected tests, constitutes the mainstay of making a correct diagnosis. Men with mild or moderate symptoms not experiencing complications are ideal candidates for medical treatment. For the rest with persistent symptoms or complications such as infection, bleeding, chronic retention or renal impairment further investigation and more invasive forms of treatment need to be considered. We review the patho-physiology of the disease, and current approaches and management of this common problem.

*Minerva Urol Nefrol. 2004 Jun;56(2):109-22*

#### **Phytotherapy for benign prostatic hyperplasia.**

**OBJECTIVE:** To systematically review the existing evidence regarding the efficacy and safety of phytotherapeutic compounds used to treat men with symptomatic benign prostatic hyperplasia (BPH). **DESIGN:** Randomized trials were identified searching MEDLINE (1966—1997), EMBASE, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. The studies were included if men had symptomatic benign prostatic hyperplasia, the intervention was a phytotherapeutic preparation alone or combined, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Key data were extracted independently by two investigators. **RESULTS:** A total of 44 studies of six phytotherapeutic agents (*Serenoa repens*, *Hypoxis rooperi*, *Secale cereale*, *Pygeum africanum*, *Urtica dioica*, *Curcubita pepo*) met inclusion criteria and were reviewed. Many studies did not report results in a method allowing meta-analysis. *Serenoa repens*, extracted from the saw palmetto, is the most widely used phytotherapeutic agent for BPH. A total of 18 trials involving 2939 men were reviewed. Compared with men receiving placebo, men taking *Serenoa repens* reported greater improvement of urinary tract symptoms and flow measures. *Serenoa repens* decreased nocturia (weighted mean difference (WMD) = -0.76 times per evening; 95% CI = -1.22 to -0.32; n = 10 studies) and improved peak urine flow (WMD = 1.93 ml s(-1); 95% CI = 0.72 to 3.14, n = 8 studies). Men treated with *Serenoa repens* rated greater improvement of their urinary tract symptoms versus men taking placebo (risk ratio of improvement = 1.72; 95% CI = 1.21 to 2.44, n = 8 studies). Improvement in symptoms of BPH was comparable to men receiving the finasteride. *Hypoxis rooperi* (n = 4 studies, 519 men) was also demonstrated to be effective in improving symptom scores and flow measures compared with placebo. For the two studies reporting the International Prostate Symptom Score, the WMD was -4.9 IPSS points (95% CI = -6.3 to -3.5, n = 2 studies) and the WMD for peak urine flow was 3.91 ml s(-1) (95% CI = 0.91 to 6.90, n = 4 studies). *Secale cereale* (n = 4 studies, 444 men) was found to modestly improve overall urological symptoms. *Pygeum africanum* (n = 17 studies, 900 men) may be a useful treatment option for BPH. However, review of the literature has found inadequate reporting of outcomes which currently limit the ability to estimate its safety and efficacy. The studies involving *Urtica dioica* and *Curcubita pepo* are limited although these agents may be effective combined with other plant extracts such as *Serenoa* and *Pygeum*. Adverse events due to phytotherapies were reported to be generally mild and infrequent. **CONCLUSIONS:** Randomized studies of *Serenoa repens*, alone or in combination with other plant extracts, have provided the strongest evidence for efficacy and tolerability in treatment of BPH in comparison with other phytotherapies. *Serenoa repens* appears to be a useful option for improving lower urinary tract symptoms and flow measures. *Hypoxis rooperi* and *Secale cereale* also appear to improve BPH symptoms although the evidence is less strong for these products. *Pygeum africanum* has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no convincing evidence supporting the use of *Urtica dioica* or *Curcubita pepo* alone for treatment of BPH. Overall, phytotherapies are less costly, well tolerated and adverse events are generally mild and infrequent. Future randomized controlled trials using standardized preparations of phytotherapeutic agents with longer study durations are needed to determine their long-term effectiveness in the treatment of BPH.

*Public Health Nutr. 2000 Dec;3(4A):459-72*

#### **Fatty fish consumption and risk of prostate cancer.**

Consumption of fatty fish might reduce the risk of prostate cancer, although epidemiological studies of fish consumption are rare. We studied the association between fish consumption and prostate cancer in a population-based prospective cohort of 6272 Swedish men. During 30 years of follow-up, men who ate no fish had a two-fold to three-fold higher frequency of prostate cancer than those who ate moderate or high amounts did. Our results suggest that fish consumption could be associated with

decreased risk of prostate cancer.

*Lancet. 2001 Jun 2;357(9270):1764-6*

### **Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma.**

Population studies have suggested that lycopene, which is mostly found in tomato and tomato products, may reduce the risk of prostate cancer. We previously found that tomato sauce consumption prior to prostatectomy for prostate cancer decreased serum prostate specific antigen, decreased oxidative DNA damage, and increased lycopene concentrations in prostate tissue (Chen et al., 2001). Here, we extended those investigations to determine whether apoptotic cell death and associated Bcl-2 and Bax proteins were modulated by tomato sauce intervention. Thirty-two patients diagnosed by biopsy with prostate carcinoma were given tomato sauce pasta entrees (30 mg lycopene/day) for 3 wk before prostatectomy. Thirty-four patients with prostate cancer who did not consume tomato sauce and underwent prostatectomy served as controls. When tumor areas with the most apoptotic cells were compared in the biopsy (before) and resected prostate tissue (after), tomato sauce consumption increased apoptotic cells in benign prostate hyperplasia (BPH) from 0.66 +/- 0.10% to 1.38 +/- 0.31% (P = 0.013) and in carcinomas from 0.84 +/- 0.13% to 2.76 +/- 0.58% (P = 0.0003). When comparable morphological areas were counted, apoptotic cell death in carcinomas increased significantly with treatment, from 0.84 +/- 0.13% to 1.17 +/- 0.19% (P = 0.028), and apoptotic cell death in BPH showed a tendency toward an increase from 0.66 +/- 0.10% to 1.20 +/- 0.32% (P = 0.20). When the values of apoptotic cells in BPH and carcinomas of patients who consume tomato sauce were compared with corresponding control lesions of the patients who did not consume tomato sauce in resected prostate tissue, the differences of values were not significant [BPH 1.38 +/- 0.31% vs. 1.14 +/- 0.32% (P = 0.97); carcinomas 2.76 +/- 0.58% vs. 1.91 +/- 0.32% (P = 0.24)]. Tomato sauce consumption did not affect Bcl-2 expression but decreased Bax expression in carcinomas. These data provide the first in vivo evidence that tomato sauce consumption may suppress the progression of the disease in a subset of patients with prostate cancer by increasing apoptotic cell death. However, because of the relatively small number of control and tomato sauce-supplemented patients and the variability in the values of apoptotic cells in BPH and carcinomas, a much larger number of patients needs to be examined to support the data generated in this study.

*Nutr Cancer. 2003;47(1):40-7*

### **Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis.**

Dietary consumption of the carotenoid lycopene (mostly from tomato products) has been associated with a lower risk of prostate cancer. Evidence relating other carotenoids, tocopherols, and retinol to prostate cancer risk has been equivocal. This prospective study was designed to examine the relationship between plasma concentrations of several major antioxidants and risk of prostate cancer. We conducted a nested case-control study using plasma samples obtained in 1982 from healthy men enrolled in the Physicians' Health Study, a randomized, placebo-controlled trial of aspirin and beta-carotene. Subjects included 578 men who developed prostate cancer within 13 years of follow-up and 1294 age- and smoking status-matched controls. We quantified the five major plasma carotenoid peaks (alpha- and beta-carotene, beta-cryptoxanthin, lutein, and lycopene) plus alpha- and gamma-tocopherol and retinol using high-performance liquid chromatography. Results for plasma beta-carotene are reported separately. Odds ratios (ORs), 95% confidence intervals (CIs), and Ps for trend were calculated for each quintile of plasma antioxidant using logistic regression models that allowed for adjustment of potential confounders and estimation of effect modification by assignment to either active beta-carotene or placebo in the trial. Lycopene was the only antioxidant found at significantly lower mean levels in cases than in matched controls (P = 0.04 for all cases). The ORs for all prostate cancers declined slightly with increasing quintile of plasma lycopene (5th quintile OR = 0.75, 95% CI = 0.54-1.06; P, trend = 0.12); there was a stronger inverse association for aggressive prostate cancers (5th quintile OR = 0.56, 95% CI = 0.34-0.91; P, trend = 0.05). In the placebo group, plasma lycopene was very strongly related to lower prostate cancer risk (5th quintile OR = 0.40; P, trend = 0.006 for aggressive cancer), whereas there was no evidence for a trend among those assigned to beta-carotene supplements. However, in the beta-carotene group, prostate cancer risk was reduced in each lycopene quintile relative to men with low lycopene and placebo. The only other notable association was a reduced risk of aggressive cancer with higher alpha-tocopherol levels that was not statistically significant. None of the associations for lycopene were confounded by age, smoking, body mass index, exercise, alcohol, multivitamin use, or plasma total cholesterol level. These results concur with a recent prospective dietary analysis, which identified lycopene as the carotenoid with the clearest inverse relation to the development of prostate cancer. The inverse association was particularly apparent for aggressive cancer and for men not consuming beta-carotene supplements. For men with low lycopene, beta-carotene supplements were associated with risk reductions comparable to those observed with high lycopene. These data provide further evidence that increased consumption of tomato products and other lycopene-containing foods might reduce the occurrence or progression of prostate cancer.

*Cancer Res. 1999 Mar 15;59(6):1225-30*

## ABSTRACTS

### Curcumin

#### **Antioxidant effect of curcumin in selenium induced cataract of Wistar rats.**

Wistar rat pups treated with curcumin, a natural constituent of *Curcuma longa* before being administered with selenium showed no opacities in the lens. The lipid peroxidation, xanthine oxidase enzyme levels in the lenses of curcumin and selenium co-treated animals were significantly less when compared to selenium treated animals. The superoxidase dismutase and catalase enzyme activities of curcumin and selenium co-treated animal lenses showed an enhancement. Curcumin co-treatment seems to prevent oxidative damage and found to delay the development of cataract.

*Indian J Exp Biol.* 2004 Jun;42(6):601-3

#### **Time- and dose-dependent effects of curcumin on gene expression in human colon cancer cells.**

**BACKGROUND:** Curcumin is a spice and a coloring food compound with a promising role in colon cancer prevention. Curcumin protects against development of colon tumors in rats treated with a colon carcinogen, in colon cancer cells curcumin can inhibit cell proliferation and induce apoptosis, it is an anti-oxidant and it can act as an anti-inflammatory agent. The aim of this study was to elucidate mechanisms and effect of curcumin in colon cancer cells using gene expression profiling. **METHODS:** Gene expression changes in response to curcumin exposure were studied in two human colon cancer cell lines, using cDNA microarrays with four thousand human genes. HT29 cells were exposed to two different concentrations of curcumin and gene expression changes were followed in time (3, 6, 12, 24, and 48 hours). Gene expression changes after short-term exposure (3 or 6 hours) to curcumin were also studied in a second cell type, Caco-2 cells. **RESULTS:** Gene expression changes (>1.5-fold) were found at all time points. HT29 cells were more sensitive to curcumin than Caco-2 cells. Early response genes were involved in cell cycle, signal transduction, DNA repair, gene transcription, cell adhesion and xenobiotic metabolism. In HT29 cells curcumin modulated a number of cell cycle genes of which several have a role in transition through the G2/M phase. This corresponded to a cell cycle arrest in the G2/M phase as was observed by flow cytometry. Functional groups with a similar expression profile included genes involved in phase-II metabolism that were induced by curcumin after 12 and 24 hours. Expression of some cytochrome P450 genes was downregulated by curcumin in HT29 and Caco-2 cells. In addition, curcumin affected expression of metallothionein genes, tubulin genes, p53 and other genes involved in colon carcinogenesis. **CONCLUSIONS:** This study has extended knowledge on pathways or processes already reported to be affected by curcumin (cell cycle arrest, phase-II genes). Moreover, potential new leads to genes and pathways that could play a role in colon cancer prevention by curcumin were identified.

*J Carcinog.* 2004 May 12;3(1):8

#### **Anticancer potential of curcumin: preclinical and clinical studies.**

Curcumin (diferuloylmethane) is a polyphenol derived from the plant *Curcuma longa*, commonly called turmeric. Extensive research over the last 50 years has indicated this polyphenol can both prevent and treat cancer. The anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumor cells, down-regulate transcription factors NF-kappa B, AP-1 and Egr-1; down-regulate the expression of COX2, LOX, NOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules and cyclin D1; down-regulate growth factor receptors (such as EGFR and HER2); and inhibit the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases. In several systems, curcumin has been described as a potent antioxidant and anti-inflammatory agent. Evidence has also been presented to suggest that curcumin can suppress tumor initiation, promotion and metastasis. Pharmacologically, curcumin has been found to be safe. Human clinical trials indicated no dose-limiting toxicity when administered at doses up to 10 g/day. All of these studies suggest that curcumin has enormous potential in the prevention and therapy of cancer. The current review describes in detail the data supporting these studies.

*Anticancer Res.* 2003 Jan-Feb;23(1A):363-98

#### **Neuroprotective effect of curcumin in middle cerebral artery occlusion induced focal cerebral ischemia in rats.**

Free radical induced neuronal damage is implicated in cerebral ischemia reperfusion (IR) injury and antioxidants are reported to have neuroprotective activity. Several in vitro and in vivo studies have proved the antioxidant potential of curcumin and its metabolites. Hence, in the present study the neuroprotective potential of curcumin was investigated in middle cerebral artery occlusion (MCAO) induced focal cerebral IR injury. 2 h of MCAO and 22 h of reperfusion resulted in the infarct volume of 210.39 +/- 31.25 mm<sup>3</sup>. Administration of curcumin 100 and 300 mg/kg, i.p. 30 min. after MCAO produced 37.23 +/- 5.10% and 46.39 +/- 10.23% (p < 0.05) reduction in infarct volume, respectively. Ischemia induced cerebral edema was reduced in a dose dependent manner. Curcumin at 300 mg/kg, i.p. produced 50.96 +/- 6.04% reduction in edema (p < 0.05) volume. Increase in lipid peroxidation after MCAO in ipsilateral and contralateral hemisphere of brain was observed, which was reduced by curcumin (300

mg/kg, i.p.)-treatment. Decrease in superoxide dismutase and glutathione peroxidase activity was observed in ipsilateral hemisphere of MCAO animal. Curcumin-treatment (300 mg/kg, i.p.) prevented IR injury mediated fall in glutathione peroxidase activity. Peroxynitrite measured using rhodamine123 fluorescence and anti-nitrotyrosine immunofluorescence indicated increased peroxynitrite formation after IR insult. Curcumin-treatment reduced peroxynitrite formation and hence the extent of tyrosine nitration in the cytosolic proteins. These results suggest the neuroprotective potential of curcumin in cerebral ischemia and is mediated through its antioxidant activity.

*Life Sci.* 2004 Jan 9;74(8):969-85

### **Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro.**

Inhibition of the accumulation of amyloid beta-peptide (Abeta) and the formation of beta-amyloid fibrils (fAbeta) from Abeta, as well as the destabilization of preformed fAbeta in the central nervous system, would be attractive therapeutic targets for the treatment of Alzheimer's disease (AD). We reported previously that nordihydroguaiaretic acid (NDGA) and wine-related polyphenols inhibit fAbeta formation from Abeta(1-40) and Abeta(1-42) and destabilize preformed fAbeta(1-40) and fAbeta(1-42) dose-dependently in vitro. Using fluorescence spectroscopic analysis with thioflavin T and electron microscopic studies, we examined the effects of curcumin (Cur) and rosmarinic acid (RA) on the formation, extension, and destabilization of fAbeta(1-40) and fAbeta(1-42) at pH 7.5 at 37 degrees C in vitro. We next compared the anti-amyloidogenic activities of Cur and RA with NDGA. Cur and RA dose-dependently inhibited fAbeta formation from Abeta(1-40) and Abeta(1-42), as well as their extension. In addition, they dose-dependently destabilized preformed fAbetas. The overall activities of Cur, RA, and NDGA were similar. The effective concentrations (EC(50)) of Cur, RA, and NDGA for the formation, extension, and destabilization of fAbetas were in the order of 0.1-1 microM. Although the mechanism by which Cur and RA inhibit fAbeta formation from Abeta and destabilize preformed fAbeta in vitro remains unclear, they could be a key molecule for the development of therapeutics for AD.

*J Neurosci Res.* 2004 Mar 15;75(6):742-50

### **Cholesterol and Alzheimer's disease: clinical and experimental models suggest interactions of different genetic, dietary and environmental risk factors.**

Alzheimer's disease (AD) is a progressive senile dementia characterized by deposition of a 4 kDa peptide of 39-42 residues known as amyloid beta-peptide (Abeta) in the form of senile plaques and the microtubule associated protein tau as paired helical filaments. Genetic studies have identified mutations in the Abeta precursor protein (APP) as the key triggers for the pathogenesis of AD. Other genes such as presenilins 1 and 2 (PS1/2) and apolipoprotein E (APOE) also play a critical role in increased Abeta deposition. Several biochemical and molecular studies using transfected cultured cells and transgenic animals point to mechanisms by which Abeta is generated and aggregated to trigger the neurodegeneration that may cause AD. Three important enzymes collectively known as 'secretases' participate in APP processing leading to the generation of either Abeta or non-amyloid proteins. However, the mechanisms of neurotoxicity of Abeta and the role of APP function in AD remain important unanswered questions. Although early studies recognized the loss of cholesterol and other lipids in the brain, these findings have been poorly connected with AD pathogenesis, despite the identification of the epsilon4 allele of APOE as a major risk factor in AD. The recent finding that cholesterol can modulate the yield of potentially toxic Abeta has boosted research on its role in AD. Consequently, several cholesterol-reducing drugs are currently being evaluated for the treatment of AD. The present review summarizes our current understanding of the relationship of AD pathogenesis with cholesterol, lipids and other genetic and environmental risk factors.

*Curr Drug Targets.* 2004 Aug;5(6):517-28

### **Curcumin inhibits dose-dependently and time-dependently neuroglial cell proliferation and growth.**

**OBJECTIVES:** Curcumin (CUR), the active chemical of the Asian spice turmeric, has strong anti-oxidant and anti-inflammatory properties. CUR inhibits proliferation and growth of several cell types, e.g. cancer cells. While CUR inhibitory effects on microglial cells are demonstrated, little is known of its effects on neuroglia, astrocytes (AST) and oligodendrocytes (OLG). Our work focuses on CUR's effects on neuroglial proliferation and growth in vitro, utilizing C-6 rat glioma 2B-clone cells, a mixed colony of both neuroglial cells, in 6 day trials. **METHODS:** The doses studied included 4, 5, 10, 15, and 20 microM - concentrations slightly smaller than those shown to stimulate protein expression in ASTs. Automated particle counter was used to determine proliferation, and marker enzyme assays were used to determine AST and OLG activity. **RESULTS:** CUR inhibited neuroglial proliferation, with the degree of inhibition correlated directly with the CUR concentration. Proliferative inhibition was observed after a concentration as low as 5 microM by day 6, while inhibition of 20 microM doses occurred by day 2 of culture. Proliferative inhibition is associated with morphological changes, e.g. cell elongation and neurite prolongation, and increased activity of a marker enzyme corresponding to differentiation of OLG and with a reduced activity of the marker enzyme for AST. **CONCLUSIONS:** Our data suggests CUR acts continuously over a period of time, with low doses being as effective as higher doses given a longer period of treatment. It has been suggested that CUR's anti-inflammatory and anti-oxidant actions may be useful in the prevention-treatment of neurodegenerative diseases, e.g. Alzheimer's and Parkinson's Diseases. Given neuroglial involvement in these diseases, and CUR's observed actions on neuroglia, the data presented here may provide further explanations of CUR's preventative-therapeutic role in these diseases.

*Neuro Endocrinol Lett.* 2003 Dec;24(6):469-7



## ABSTRACTS

### Selenium

#### **Molecular actions of selenium in the brain: neuroprotective mechanisms of an essential trace element.**

In addition to acting as an essential nutrient for the immune system and overall body function, it is apparent that selenium also plays a critical role in the operation of the nervous system. Selenium itself is a constituent of selenoproteins, which are primarily involved in antioxidant function and redox status. However, apart from its covalent incorporation into these proteins, selenium also performs neuroprotective actions independent of translational processes. Furthermore, low selenium intake has detrimental effects on proper brain function, such as epileptic episodes and neuronal cell death, which have, in turn, been shown to be mitigated by higher selenium levels. Understanding the mechanisms of selenium action will be crucial to determining its potential as a preventive and therapeutic agent against excitatory brain damage.

*Rev Neurosci. 2004;15(1):19-32*

#### **The neurobiology of selenium: lessons from transgenic mice.**

The brain represents a privileged organ with respect to selenium (Se) supply and retention. It contains high amounts of this essential trace element, which is efficiently retained even in conditions of Se deficiency. Accordingly, no severe neurological phenotype has been reported for animals exposed to Se-depleted diets. They are, however, more susceptible to neuropathological challenges. Recently, gene disruption experiments supported a pivotal role for different selenoproteins in brain function. Using these and other transgenic models, longstanding questions concerning the preferential supply of Se to the brain and the hierarchy among the different selenoproteins are readdressed. Given that genes for at least 25 selenoproteins have been identified in the human genome, and most of these are expressed in the brain, their specific roles for normal brain function and neurological diseases remain to be elucidated.

*J Nutr. 2004 Apr;134(4):707-10*

#### **How HIV-1 causes AIDS: implications for prevention and treatment.**

HIV-1 encodes for one of the human glutathione peroxidases. As a consequence, as it is replicated, its genetic needs cause it to deprive HIV-1 seropositive individuals not only of glutathione peroxidase, but also of the four basic components of this selenoenzyme, namely selenium, cysteine, glutamine, and tryptophan. Eventually this depletion process causes severe deficiencies of all these substances. These, in turn, are responsible for the major symptoms of AIDS which include immune system collapse, greater susceptibility to cancer and myocardial infarction, muscle wasting, depression, diarrhea, psychosis and dementia. As the immune system fails, associated pathogenic cofactors become responsible for a variety of their own unique symptoms. Any treatment for HIV/AIDS must, therefore, include normalization of body levels of glutathione, glutathione peroxidase, selenium, cysteine, glutamine, and tryptophan. Although various clinical trials have improved the health of AIDS patients by correcting one or more of these nutritional deficiencies, they have not, until the present, been addressed together. Physicians involved in a selenium and amino-acid field trial in Botswana, however, are reporting that this nutritional protocol reverses AIDS in 99% of patients receiving it, usually within three weeks.

*Med Hypotheses. 2004;62(4):549-53*

#### **Making sense of sex and supplements: differences in the anticarcinogenic effects of selenium in men and women.**

The role of the essential trace mineral selenium in human health and disease is currently a subject of intense interest. In particular, the possible cancer preventive effects of dietary selenium supplementation are now being investigated in several large, randomized trials. The association between selenium status, genotoxic damage, and cancer risk remains enigmatic because epidemiologic studies have failed to consistently link low selenium status with increased cancer risk in men and women. In this paper, we considered the evidence that there are sex-based differences in the anticarcinogenic effects of selenium in humans. We focused our review on prospective human studies in which the relationship between selenium status and cancer risk in men and women was directly compared. Results from cohort studies conducted in seven countries (Belgium, China, Finland, Japan, Netherlands, Norway, and United States) were used to assess the strength of association between low selenium status and the incidence of all cancers, sex-specific cancers, and cancers at particular anatomic sites. In general, the available data support the hypothesis that cancer risk in men is more profoundly influenced by selenium status than cancer risk in women. Factors contributing to the apparent difference in the effects of selenium on cancer incidence in men and women may include sex-based differences in the metabolism and/or tissue distribution of selenium, as well as sex- or gender-related factors that influence tumor biology. Studies are needed to further define the dose-response relationship between selenium and cancer risk in men and women. A more complete understanding of the mechanisms by which selenium modulates cancer initiation and progression is needed to optimize dietary selenium supplementation as a practical cancer preventive strategy. Ultimately, achieving the ambitious goal of cancer prevention may require sex- and gender-specific approaches.

### **Neurological dysfunction occurs in mice with targeted deletion of the selenoprotein P gene.**

Brain function and selenium concentration are well maintained in rodents under conditions of selenium deficiency. Recently, however, targeted deletion of the selenoprotein P gene (Sepp) has been associated with a decrease in brain selenium concentration and with neurological dysfunction. Studies were conducted with Sepp(-/-) and Sepp(+/-) mice to characterize the neurological dysfunction and to correlate it with dietary selenium level. When weanling Sepp(-/-) mice were fed the basal diet (<0.01 mg/kg selenium) supplemented with 0, 0.05 or 0.10 mg selenium/kg, they developed spasticity that progressed and required euthanasia. Supplementing the diet with > or =0.25 mg selenium/kg prevented the neurological dysfunction. To determine whether neurological dysfunction would occur in more mature Sepp(-/-) mice deprived of selenium, Sepp(-/-) mice that had been fed the basal diet supplemented with 1.0 mg selenium/kg for 4 wk were switched to a selenium-deficient diet. Within 3 wk they had developed neurological dysfunction and weight loss. At 3 wk, the 1.0 mg selenium/kg diet was reinstated. Neurological function stabilized but did not return to normal. Brain selenium concentration did not increase. Weight gain resumed. This study shows that neurological dysfunction occurs when selenium supply to the brain is curtailed and that the dysfunction is not readily reversible. Both the absence of selenoprotein P and a low dietary selenium supply are necessary for the dysfunction to occur, indicating that selenoprotein P and at least one other form of selenium supply the element to the brain.

*J Nutr.* 2004 Jan;134(1):157-61

### **The controversy surrounding selenium and cardiovascular disease: a review of the evidence.**

Selenium is an essential trace element that is an integral part of many proteins, with catalytic and structural functions. The antioxidant properties of some selenoproteins, such as glutathione peroxidase, may be particularly important in carcinogenesis and heart disease. The content of selenium in food depends on the selenium content of the soil where the plants are grown or the animals are raised. Moreover, the metabolism of selenium is determined by its dietary form: some forms are better utilized than others. Therefore, wide variations have been found in selenium status in different parts of the world. In animal studies, selenium deficiency is associated with cardiomyopathy and sudden death, as well as reduced T-cell counts and impaired lymphocyte proliferation and responsiveness. Abnormalities in liver function, brain, heart, striated muscle, pancreas and genital tract have also been reported. In humans, selenium deficiency has been implicated in the etiology of cardiovascular disease and other conditions in which oxidative stress and inflammation are prominent features, but there is still only limited evidence from epidemiological and ecological studies for this, and the therapeutic benefit of selenium administration in the prevention and treatment of cardiovascular diseases remains insufficiently documented. Interventions studies are currently in progress to assess the benefits of selenium supplements in primary and secondary prevention of atherosclerosis. The results to date are inconclusive and further controlled trials are needed.

*Med Sci Monit.* 2003 Jan;9(1):RA9-18

### **Selenium and selenoproteins in the brain and brain diseases.**

Over the past three decades, selenium has been intensively investigated as an antioxidant trace element. It is widely distributed throughout the body, but is particularly well maintained in the brain, even upon prolonged dietary selenium deficiency. Changes in selenium concentration in blood and brain have been reported in Alzheimer's disease and brain tumors. The functions of selenium are believed to be carried out by selenoproteins, in which selenium is specifically incorporated as the amino acid, selenocysteine. Several selenoproteins are expressed in brain, but many questions remain about their roles in neuronal function. Glutathione peroxidase has been localized in glial cells, and its expression is increased surrounding the damaged area in Parkinson's disease and occlusive cerebrovascular disease, consistent with its protective role against oxidative damage. Selenoprotein P has been reported to possess antioxidant activities and the ability to promote neuronal cell survival. Recent studies in cell culture and gene knockout models support a function for selenoprotein P in delivery of selenium to the brain. mRNAs for other selenoproteins, including selenoprotein W, thioredoxin reductases, 15-kDa selenoprotein and type 2 iodothyronine deiodinase, are also detected in the brain. Future research directions will surely unravel the important functions of this class of proteins in the brain.

*J Neurochem.* 2003 Jul;86(1):1-12

treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.