

34 Se Selenium	35 Br Bromine
52 Te Tellurium	53 I Iodine

## Selenium

### Introduction

Until the late 1950s, selenium was believed to be a toxic element. In 1957, Schwarz and Foltz established selenium as an essential trace element in the diet for the prevention of disease.<sup>1</sup> In food, selenium is derived from both vegetable and animal products, particularly seafood, liver, and cereals.

### Biochemistry

As a member of the sulfur family of elements, selenium shares several chemical properties with sulfur, including valence states and the ability to form covalent bonds with carbon.<sup>1</sup>

### Pharmacokinetics

Selenium levels in the body are largely dependent on the amount of the element in the diet. However, the form of selenium within the diet has an important influence on absorption. L-(+)selenomethionine is readily absorbed from the gastrointestinal tract and is significantly better absorbed and retained in the body than inorganic selenium in the form of selenite. L-(+)selenomethionine has slower whole-body turnover compared with selenite, an attribute that provides efficient use of the selenium contained in the complex methionine.<sup>2</sup> In rats, dietary supplementation with selenomethionine, selenite, and selenocysteine showed the highest increase in tissue selenium levels was accomplished with selenomethionine, with tissue selenium increase most significant in muscles.<sup>3</sup>

### Mechanisms of Action

Selenium is most notable for its antioxidant properties. In 1973, Rotruck and colleagues provided rationale for identifying selenium as an antioxidant.<sup>4</sup> The selenium-dependent enzyme glutathione peroxidase (GPX) recycles glutathione, reducing lipid peroxidation by catalyzing the reduction of peroxides, including hydrogen peroxide. Selenium is a cofactor within several metabolic pathways, including the GPX pathway, where it is present as selenocysteine.

After selenium has been metabolized to its bioactive metabolites – methylselenium and S-methylselenocysteine – it appears to act at the level of transcription factor NFκB,<sup>5</sup> signal transduction,<sup>6,7</sup> cell cycle checkpoints,<sup>8</sup> and enhanced apoptosis.<sup>9</sup> Evidence also indicates selenium may substitute for sulfur in key signaling enzymes such as tyrosine kinase.<sup>10</sup> Therefore, selenium's chemopreventive role is not limited to its antioxidant function.

Iodothyronine deiodinase (ID) is an enzyme involved in thyroid hormone metabolism, specifically in the conversion of T4 to T3. There are three isoforms associated with tissue distribution. A number of authors have noted an association between selenium status and low plasma T3 levels, reflecting decreased ID activity.<sup>11</sup> Studies show there may be decreased T4 levels following selenium administration, suggesting the importance of correct dosing of this nutrient.<sup>12,13</sup> Plasma selenium concentrations less than 67 μg/L were found to be associated with impaired peripheral conversion of T4 to T3.<sup>14</sup>

The enzyme thioredoxin reductase (TR), an NADPH-dependent flavoenzyme involved in intracellular reduction of substrates, has been determined to be a selenium-dependent enzyme. Results collected in animal cell lines suggest it is an indicator of selenium intake, but its localization limits its use as a clinically relevant indicator of selenium status.<sup>15,16</sup> Supranutritional quantities of selenium given to rats or administered to human cancer cell lines can directly increase the specific activity of this enzyme.<sup>17</sup> It has been suggested that TR is the selenoprotein involved in the anticancer effects observed for some forms of selenium at supranutritional doses.<sup>18</sup>

## Deficiency States

Selenium deficiency has been well documented in the pathogenesis and pathology of Keshan disease, a multifocal myocarditis occurring in the Chinese province of Keshan, where the soil lacks selenium.<sup>19</sup> Epidemiological investigations in Finland, also a low-selenium area, have found an association between low nutritional selenium status and increased risk of cardiovascular disease.<sup>20</sup> The following clinical and laboratory manifestations of selenium deficiency have been described: myositis, whitening of the fingernail beds,<sup>21</sup> psuedoalbinism, elevated creatine kinase derived from muscles, macrocytosis,<sup>22</sup> and osteoarthropathy, known as Kashin-Beck disease.<sup>23</sup>

An inverse relationship has been observed between serum selenium levels and carcinogenesis in various sites of the body, including the liver, mammary gland, esophagus, stomach, colon, rectum, lung, urinary tract, prostate, female reproductive organs, thyroid, hematological system, oral cavity, pharynx, and skin.<sup>24</sup> Several other conditions appear to have an inverse relationship with regard to levels of environmental selenium (in soil) and the occurrence of disease, including endemic goiter, sudden infant death syndrome, multiple sclerosis,<sup>25</sup> and schizophrenia.<sup>26</sup>

## Clinical Indications

### Cancer

The connection between selenium and cancer was originally demonstrated by correlation studies relating selenium levels in crops and cancer mortality rates<sup>27</sup> and epidemiological studies linking increased cancer risk with low blood selenium levels.<sup>28</sup> In 1976, Broghamer reported that, "Lower selenium levels in patients with carcinoma are likely to be associated with (1) distant metastasis; (2) multiple primary tumors; (3) multiple recurrences; and (4) short survival time."<sup>29</sup>

The Nutritional Prevention of Cancer Trial, a randomized clinical study, was designed to evaluate the efficacy of selenium as selenized yeast (200 µg/day) in preventing the recurrence of nonmelanoma skin cancer among 1,312 residents of the eastern United States. Original secondary analyses showed striking inverse relationships between treatment and the incidence of total, lung, prostate, and colorectal cancer, and total cancer mortality. Results showed selenium supplementation reduced total and prostate cancer incidence, but was not significantly associated with lung and colorectal cancer incidence. The protective effect of selenium was confined to males and was most pronounced in former smokers.<sup>30</sup>

Current interest in the relationship between selenium and prostate cancer is based largely on a landmark, 1996 clinical intervention study by Clark et al<sup>31,32</sup> that demonstrated supplementation with 200 µg selenium/day in the form of selenized yeast resulted in a 60-percent decrease in prostate cancer over a mean period of 4.5 years. Studies by the same authors are currently underway to evaluate the use of selenium supplementation at different points during the development of cancerous prostatic tissue.<sup>33</sup>

### HIV/AIDS

Selenium and glutathione may play a role in modifying HIV infection *in vitro* and *in vivo*. According to a theory proposed by Taylor and colleagues,<sup>34</sup> HIV may carry several genes with the potential to encode selenoproteins, one of which appears to have a propensity to bind with DNA, acting as a repressor of HIV viral

transcription. This mechanism could result in turning off expression of HIV, thus slowing virus proliferation. In a study of 45 HIV-infected patients, 14 received oral selenium (100 µg), 13 received oral beta-carotene (60 mg), and 18 received no supplementation. All patients were evaluated with regard to the blood antioxidant system, specifically superoxide dismutase (SOD) and glutathione peroxidase. GPX activity increased significantly following selenium supplementation, whereas there was only a slight increase in the beta-carotene group.<sup>35</sup> No significant difference was found in levels of SOD when compared to baseline.

Selenium deficiency, more than any other nutrient, has been documented to correlate with progression and mortality of HIV.<sup>36</sup> A study of 104 HIV-positive individuals found a progressive deficiency of selenium, erythrocyte glutathione peroxidase, and plasma glutathione was associated with progression of the disease.<sup>37</sup> Selenium deficiencies have also been documented more frequently in patients with severe cases of AIDS and AIDS-related complex than in asymptomatic HIV patients.<sup>38,39</sup> The impact of selenium status in the development of mycobacterial disease in HIV-1 seropositive drug users was investigated over a two-year period. Multivariate analyses, controlling for antiretroviral treatment and CD4-cell count, revealed body mass index and selenium level were significant factors in the relative risk for disease development.<sup>40</sup>

### *Hepatitis/Liver Disease*

Selenium levels appear to be severely depleted in individuals suffering from liver disease, specifically cirrhosis and hepatitis. In one study of 50 individuals with liver disease, serum selenium levels were significantly lower when compared to a control group and selenium levels were lower in individuals with cirrhosis (n=12) when compared to those with hepatitis (n=38), due to a decrease in liver function in cirrhotic individuals. Low selenium levels also were correlated with increased total serum cholesterol levels as well as gamma-glutamyl-transferase levels.<sup>41</sup>

### *Rheumatoid Arthritis*

Rheumatoid arthritis, characterized by migration of activated phagocytes and leukocytes, appears to be an inflammatory condition with marked selenium deficiency.<sup>42,43</sup> The results of a double-blind study found supplementing 200 µg/day selenium for three months significantly reduced painful joint involvement.<sup>44</sup> A follow-up, double-blind study using the same dose and duration did not replicate these results as the placebo group also showed improvement.<sup>45</sup>

### *Cardiomyopathy*

Keshan disease, cardiomyopathy named for Keshan County in China where the disease was first discovered, can be reversed by selenium replacement. A prospective study was conducted under strict control among children in endemic districts of Sichuan Province from 1974-1977.<sup>46</sup> The results clearly showed that selenium, as sodium selenite, not only reduced the morbidity and mortality of Keshan disease, but also reduced cardiac damage. Other forms of cardiomyopathy have also similarly been linked to selenium deficiency.<sup>47</sup>

### *Asthma*

Many dietary factors have been implicated in the etiology of chronic obstructive pulmonary disease, particularly asthma.<sup>48</sup> Reduced blood selenium levels have consistently been observed in adults with asthma.<sup>49</sup> A higher intake of selenium may suppress asthma inflammation by saturating GPX. A population-based study has found that asthma was less common in adults who consumed more apples and who had a higher intake of selenium. Further, selenium appeared to be associated with prevalence of disease, but not severity.<sup>50</sup> The International Study of Asthma and Allergies in Childhood (ISAAC) found evidence that selenium-rich foods, such as fish and cereals/whole grains, may protect against asthma in children.<sup>51</sup> A pilot study of 17 corticosteroid-dependent asthmatics found reduced use of both inhaled and systemic corticosteroids after supplementing with a daily dose of 200 µg selenium. Reduced consumption of inhaled corticosteroids occurred after 24-96 weeks of supplementation, while systemic corticosteroid use decreased after 48 weeks.<sup>52</sup>

### *Myotonic Dystrophy*

To date, very few options are available for the treatment of myotonic dystrophy. It has been hypothesized increased levels of free radicals and lipid peroxides may play an important role in the pathogenesis of this disease. In one study, serum selenium levels appeared to be decreased in this population.<sup>53</sup> In several small studies, selenium supplementation seemed to have an effect on myotonia. In one study, relaxation time decreased in muscle groups by 50 percent, while muscle strength slightly increased; however, there was no overall improvement in motor performance.<sup>54</sup> A series of studies by Orndahl et al demonstrated daily doses of selenium ranging from 1.6-4 mg in combination with 600-800 mg vitamin E resulted in improvements in grip strength, gait, and walking speed.<sup>55-57</sup>

### *Male Infertility*

Selenium has been long recognized as essential for successful human reproduction as it is required for sperm maturation and motility, and may reduce the risk of miscarriage.<sup>58</sup> The selenoprotein phospholipid hydroperoxide glutathione peroxidase (PHGPx) accounts for nearly the entire selenium content of mammalian testes. Increased PHGPx levels are associated with increased viability, morphologic integrity, and motility of sperm.<sup>59</sup> Human studies have shown low dose (3.5 µg/kg/day) selenium supplementation to be effective in the correction of male infertility.<sup>60</sup> One study demonstrated low dose, short-term selenium supplementation was more effective in the treatment of male infertility than high dose supplementation, which appeared to affect thyroid metabolism, decreasing sperm motility.<sup>61</sup> Dietary selenium was 47 µg/day for the first 21 days, then either 13 µg/day or 297 µg/day. The fraction of motile sperm in the high-dose selenium group decreased by 32 percent by week 13 and ended 18 percent lower than baseline.

### *Heavy Metal Toxicity*

Selenium may have a protective effect against mercury and other heavy metal toxicities.<sup>62,63</sup> Experimental findings have shown that

selenium-deficient rodents are more susceptible to the prenatal toxicity of methylmercury. In the neonate, significant alterations of the activities of selenoenzymes, such as glutathione peroxidase and iodothyronine deiodinases, were evident.<sup>64</sup>

Selenium appears to antagonize cadmium, especially in acute exposures. In a mouse study, after acute cadmium exposure a significant decrease in cadmium levels was observed in the kidneys and liver following an eight-week daily selenium supplementation.<sup>65</sup>

### *Hypothyroidism*

In a randomized, prospective, blinded study in patients with autoimmune thyroiditis, selenium supplementation of 200 µg/day for three months decreased thyroid (peroxidase) specific antibodies (TPOAb) from 100 percent to 63.6 percent. Even more importantly, nine of 36 patients had complete normalization of TPOAb concentrations, while thioredoxin reductase levels reduced only slightly.<sup>66</sup> Plasma TPOAb level is thought to be specific for autoimmune thyroiditis, as it reflects thyroid inflammation.

### *Cataracts*

Oxidation of lens proteins is part of the pathophysiology of cataracts. A decrease in glutathione peroxidase has been found in the lenses of selenium-deficient rats. Additionally, an increase in free radicals was also noted in both selenium- and vitamin E-deficient groups.<sup>67</sup> Evaluation of selenium levels in humans has found lower than normal levels in sera and aqueous humor in cataract patients.<sup>68</sup>

### *Food Intolerance*

Low selenium status has been demonstrated in several malabsorptive syndromes and in some digestive and allergic conditions.<sup>69,70</sup> Plasma selenium concentrations in healthy children were compared to those with food allergies. Selenium levels in healthy children averaged 71.8 mg/L; whereas, in those with food allergy, levels averaged 54.1 mg/L (with less intestinal villus atrophy) or 50.4 mg/L (with greater intestinal villus atrophy). Results show children with food allergy display higher risk of selenium deficiency.<sup>71</sup>

### Other Clinical Indications

Selenium supplementation has also been shown to be effective in treatment and prevention of several other conditions, including sudden infant death syndrome,<sup>72,73</sup> cystic fibrosis,<sup>74</sup> otitis media,<sup>75</sup> and celiac disease.<sup>76</sup> Supplementation may also be effective in slowing the aging process<sup>77,78</sup> and for mood enhancement.<sup>79</sup>

### Drug-Nutrient and Nutrient-Nutrient Interactions

Interactions between selenium and other dietary constituents may affect the biological properties of selenium. In some studies, selenium, when supplemented with vitamin A, provided an added protective effect against breast cancer.<sup>80</sup>

Vitamin C may interfere with the protective effects of some forms of selenium. In one study, selenomethionine and selenite, when used alone were equally effective against chemically induced mammary carcinoma in rats. The protective effect of selenite was nullified by supplementation with vitamin C; the protective effect of selenomethionine, however, was not affected by vitamin C.<sup>81</sup> It has been postulated that selenite is reduced by vitamin C to elemental selenium and is therefore poorly absorbed. There are no known drug interactions with selenium.

### Side Effects and Toxicity

Selenium may have toxic effects at levels only four to five times that normally ingested in the human diet. Epidemiological studies and case reports have shown chronic exposure to selenium compounds is associated with several adverse health effects in humans. An early toxic effect of selenium is a disruption of endocrine function, particularly the synthesis of thyroid hormones, but additionally on the metabolism of growth hormone and insulin-like growth factor. High levels of dietary selenium (in a seleniferous area in Venezuela) were significantly associated with decreased T3 levels, suggesting activity of ID is depressed in conditions with high intake, i.e., more than 350 µg/day.<sup>82</sup>

Other adverse effects of high dose, chronic selenium exposure may be the impairment of natural killer cells, and at extremely high levels hepatotoxicity and gastrointestinal disturbances. There have also been reported cases of dermatological effects such as nail and hair loss and dermatitis following long-term environmental exposure.<sup>83</sup>

### Dosage

In the United States an intake for men and women of 55 µg per day with an upper safe level of 400 µg per day is recommended.<sup>84</sup> In the United Kingdom, a Required Nutritional Intake (RNI) of 60 µg per day for women and 75 µg per day for men has been set.<sup>85</sup> No long-term follow-up was noted with the high doses (1.6-4 mg) used for myotonic dystrophy.

### References

1. Schwarz S. Essentiality and metabolic functions of selenium. *Med Clin North Am* 1976;60:745-758.
2. Swanson CA, Patterson BH, Levander OA, et al. Human [74Se]selenomethionine metabolism: a kinetic model. *Am J Clin Nutr* 1991;54:917-926.
3. Deagen JT, Butler JA, Beilstein MA, Whanger PD. Effects of dietary selenite, selenocysteine and selenomethionine on selenocysteine lyase and glutathione peroxidase activities and on selenium levels in rat tissues. *J Nutr* 1987;117:91-98.
4. Rotruck JT, Pope AL, Ganther HE, et al. Selenium: biochemical role as a component of glutathione peroxidase. *Science* 1973;179:588-590.
5. Markopoulos V, Bruning T, Schulze-Osthoff K. Selenium-mediated inhibition of transcription factor NF-kappa B and HIV-1 LTR promoter activity. *Arch Toxicol* 1996;70:277-283.
6. Stapleton SR, Garlock GL, Foellmi-Adams L, Kletzien RF. Selenium: potent stimulator of tyrosyl phosphorylation and activator of MAP kinase. *Biochem Biophys Acta* 1997;1355:259-269.
7. Adler V, Pincus MR, Posner S, et al. Effects of chemopreventive selenium compounds on Jun N-kinase activities. *Carcinogenesis* 1996;17:1849-1854.

8. Kaeck M, Lu J, Strange R, et al. Differential induction of growth arrest inducible genes by selenium compounds. *Biochem Pharmacol* 1997;53:921-926.
9. Lu J, Kaeck M, Jiang C, et al. Selenite induction of DNA strand breaks and apoptosis in mouse leukemic L 1210 cells. *Biochem Pharmacol* 1994;47:1531-1535.
10. Gopalakrishna R, Gundimeda U, Chen ZH. Cancer-preventive selenocompounds induce a specific redox modification of cysteine-rich regions in Ca(2+)-dependent isoenzymes of protein kinase C. *Arch Biochem Biophys* 1997;348:25-36.
11. Strain JJ, Bokje E, van't Veer P, et al. Thyroid hormones and selenium status in breast cancer. *Nutr Cancer* 1997;27:48-52.
12. Olivieri O, Girelli D, Azzini M, et al. Low selenium status in the elderly influences thyroid hormones. *Clin Sci (Lond)* 1995;89:637-642.
13. Calomme MR, Vanderpas JB, Francois B, et al. Thyroid function parameters during a selenium repletion/depletion study in phenylketonuric subjects. *Experientia* 1995;51:1208-1215.
14. Duffield AJ, Thomson CD, Hill KE, Williams S. An estimation of selenium requirements for New Zealanders. *Am J Clin Nutr* 1999;70:896-903.
15. Hill KE, McCollum GW, Boeglin ME, Burk RF. Thioredoxin reductase activity is decreased by selenium deficiency. *Biochem Biophys Res Commun* 1997;234:293-295.
16. Allan CB, Lacourciere GM, Stadtman TC. Responsiveness of selenoproteins to dietary selenium. *Annu Rev Nutr* 1999;19:1-16.
17. Berggren MM, Mangin JF, Gasdaka JR, Powis G. Effect of selenium on rat thioredoxin reductase activity: increase by supranutritional selenium and decrease by selenium deficiency. *Biochem Pharmacol* 1999;57:187-193.
18. Ganther HE. Selenium metabolism, selenoproteins and mechanisms of cancer prevention: complexities with thioredoxin reductase. *Carcinogenesis* 1999;20:1657-1666.
19. Li GS, Wang F, Kang D, Li C. Keshan disease: an endemic cardiomyopathy in China. *Hum Pathol* 1985;16:602-609.
20. Salonen JT, Afthan G, Huttunen JK, et al. Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study. *Lancet* 1982;2:175-179.
21. Kien CL, Ganther HE. Manifestations of chronic selenium deficiency in a child receiving total parenteral nutrition. *Am J Clin Nutr* 1983;37:319-328.
22. Vinton NE, Dahlstrom KA, Strobel CT, Ament ME. Macrocytosis and pseudoalbuminism: manifestations of selenium deficiency. *J Pediatr* 1987;111:711-717.
23. Yang GQ, Ge KY, Chen JS, Chen XS. Selenium-related endemic diseases and the daily selenium requirement of humans. *World Rev Nutr Diet* 1988;55:98-152.
24. Garland M, Stamper MJ, Willett WC, Hunter DJ. The epidemiology of selenium and human cancer. In: Frei B, ed. *Natural Antioxidants in Human Health and Disease*. San Diego, CA: Academic Press; 1994:263-281.
25. Foster HD. The iodine-selenium connection: its possible roles in intelligence, cretinism, sudden infant death syndrome, breast cancer and multiple sclerosis. *Med Hypotheses* 1993;40:61-65.
26. Foster HD. The geography of schizophrenia: possible links with selenium and calcium deficiencies, inadequate exposure to sunlight and industrialization. *J Orthomolecular Med* 1988;3:135-140.
27. el-Bayoumy K, Upadhyaya P, Chae YH, et al. Chemoprevention of cancer by organoselenium compounds. *J Cell Biochem Suppl* 1995;22:92-100.
28. Nomura AM, Lee J, Stemmermann GN, Combs GF Jr. Serum selenium and subsequent risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2000;9:883-887.
29. Broghamer WL. Relationship between serum selenium levels and patients with carcinoma. *Cancer* 1976;37:1384-1388.
30. Duffield-Lillico AJ, Reid ME, Turnbull BW, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. *Cancer Epidemiol Biomarkers Prev* 2002;11:630-639.

31. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* 1996;276:1957-1963.
32. Clark LC, Dalkin B, Krongrad A, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998;81:730-734.
33. Nelson MA, Reid M, Duffield-Lillico AJ, Marshall JR. Prostate cancer and selenium. *Urol Clin North Am* 2002;29:67-70.
34. Taylor EW, Ramanathan CS, Jalluri RK, Nadimpalli RG. A basis for new approaches to the chemotherapy of AIDS: novel genes in HIV-1 potentially encode selenoproteins expressed by ribosomal frameshifting and termination suppression. *J Med Chem* 1994;37:2637-2654.
35. Delmas-Beauvieux MC, Peuchant E, Couchouron A, et al. The enzymatic antioxidant system in blood and glutathione status in human immunodeficiency virus (HIV)-infected patients: effects of supplementation with selenium or beta-carotene. *Am J Clin Nutr* 1996;64:101-107.
36. Baum MK, Shor-Posner G, Lai S, et al. High risk of HIV-related mortality is associated with selenium deficiency. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;15:370-374.
37. Look MP, Rockstroh JK, Rao GS, et al. Serum selenium, plasma glutathione (GSH) and erythrocyte glutathione peroxidase (GSH-Px)-levels in asymptomatic versus symptomatic human immunodeficiency virus-1 (HIV-1)-infection. *Eur J Clin Nutr* 1997;51:266-272.
38. Cirelli A, Ciardi M, de Simone C, et al. Serum selenium concentration and disease progress in patients with HIV infection. *Clin Biochem* 1991;24:211-214.
39. Constans J, Sire S, Sergeant C, et al. Dilated cardiomyopathy and selenium deficiency in AIDS. Apropos of a case. *Rev Med Interne* 1997;18:642-645. [Article in French]
40. Shor-Posner G, Miguez MJ, Pineda LM, et al. Impact of selenium status on the pathogenesis of mycobacterial disease in HIV-1-infected drug users during the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2002;29:169-173.
41. Navarro-Alarcon M, Lopez-Ga de la Serrana H, Perez-Valero V, Lopez-Martinez MC. Selenium concentrations in serum of individuals with liver diseases (cirrhosis or hepatitis): relationship with some nutritional and biochemical markers. *Sci Total Environ* 2002;291:135-141.
42. Aaseth J, Haugen M, Forre O. Rheumatoid arthritis and metal compounds – perspectives on the role of oxygen radical detoxification. *Analyst* 1998;123:3-6.
43. Kose K, Dogan P, Kardas Y, Saraymen R. Plasma selenium levels in rheumatoid arthritis. *Biol Trace Elem Res* 1996;53:51-56.
44. Peretz A, Neve J, Duchateau J, Famaey JP. Adjuvant treatment of recent onset rheumatoid arthritis by selenium supplementation: preliminary observations. *Br J Rheumatol* 1992;31:281-282.
45. Peretz A, Siderova V, Neve J. Selenium supplementation in rheumatoid arthritis investigated in a double blind, placebo-controlled trial. *Scand J Rheumatol* 2001;30:208-212.
46. Ge K, Yang G. The epidemiology of selenium deficiency in the etiological study of endemic disease in China. *Am J Clin Nutr* 1993;57:259S-263S.
47. Rivera MT, de Souza AP, Moreno AH, et al. Progressive Chagas' cardiomyopathy is associated with low selenium levels. *Am J Trop Med Hyg* 2002;66:706-712.
48. Romieu I, Trenga C. Diet and obstructive lung disease. *Epidemiol Rev* 2001;23:268-287.
49. Fogarty A, Britton J. The role of diet in the aetiology of asthma. *Clin Exp Allergy* 2000;30:615-627.
50. Shaheen SO, Sterne JA, Thompson RL, et al. Dietary antioxidants and asthma in adults: population-based case-control study. *Am J Respir Crit Care Med* 2001;164:1823-1828.
51. Ellwood P, Asher MI, Bjorksten B, et al. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISAAC Phase One Study Group. *Eur Respir J* 2001;17:436-443.
52. Gazdik F, Kadrabova J, Gazdikova K. Decreased consumption of corticosteroids after selenium supplementation in corticoid-dependent asthmatics. *Bratisl Lek Listy* 2002;103:22-25.

53. Ihara Y, Mori A, Hayabara T, et al. Free radicals, lipid peroxides and antioxidants in blood of patients with myotonic dystrophy. *J Neurol* 1995;242:119-122.
54. Backman E, Henriksson KG. Effect of sodium selenite and vitamin E treatment in myotonic dystrophy. *J Intern Med* 1990;228:577-581.
55. Orndahl G, Sellden U, Hallin S, et al. Myotonic dystrophy treated with selenium and vitamin E. *Acta Med Scand* 1986;219:407-414.
56. Orndahl G, Rindby A, Selin E. Selenium therapy of myotonic dystrophy. *Acta Med Scand* 1983;213:237-239.
57. Orndahl G, Grimby G, Grimby A, et al. Functional deterioration and selenium-vitamin E treatment in myotonic dystrophy. A placebo-controlled study. *J Intern Med* 1994;235:205-210.
58. Rayman MP, Rayman MP. The argument for increasing selenium intake. *Proc Nutr Soc* 2002;61:203-215.
59. Foresta C, Flohe L, Garolla A, et al. Male fertility is linked to the selenoprotein phospholipid hydroperoxide glutathione peroxidase. *Biol Reprod* 2002;67:967-971.
60. Nikolaev AA, Lutskii DL, Lozhkina LV, et al. Selenium correction of male subfertility. *Urologiia* 1999;4:29-32. [Article in Russian]
61. Hawkes WC, Turek PJ. Effects of dietary selenium on sperm motility in healthy men. *J Androl* 2001;22:764-772.
62. Whanger PD. Selenium and heavy metal toxicity. In: Spallholz JE, Martin JL, Ganther HE, eds. *Selenium in Biology and Medicine*. Westport, CT: AVI; 1981:230-255.
63. Diplock AT, Watkins WJ, Hewison M. Selenium and heavy metals. *Ann Clin Res* 1986;18:55-60.
64. Watanabe C. Selenium deficiency and brain functions: the significance for methylmercury toxicity. *Nippon Eiseigaku Zasshi* 2001;55:581-589. [Article in Japanese]
65. Jamba L, Nehru B, Bansal MP. Selenium supplementation during cadmium exposure: changes in antioxidant enzymes and the ultrastructure of the kidney. *J Trace Elem Exp Med* 1997;10:233-242.
66. Gartner R, Gasnier BC, Dietrich JW, et al. Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. *J Clin Endocrinol Metab* 2002;87:1687-1691.
67. Cai QY, Chen XS, Zhu LZ, et al. Biochemical and morphological changes in the lenses of selenium and/or vitamin E deficient rats. *Biochem Environ Sci* 1994;7:109-115.
68. Karakucuk S, Ertugrul Mirza G, Faruk Ekinciler O, et al. Selenium concentrations in serum, lens and aqueous humour of patients with senile cataract. *Acta Ophthalmol Scand* 1995;73:329-332.
69. Thomas AG, Miller V, Shenkin A, et al. Selenium and glutathione peroxidase status in paediatric health and gastrointestinal disease. *J Pediatr Gastroenterol Nutr* 1994;19:213-219.
70. Rannem T, Ladefoged K, Hylander E, et al. Selenium depletion in patients with gastrointestinal diseases: are there any predictive factors? *Scand J Gastroenterol* 1998;33:1057-1061.
71. Kalita B, Nowak P, Slimok M, et al. Selenium plasma concentration level in children with food allergy. *Pol Merkuriusz Lek* 2001;10:411-413. [Article in Polish]
72. McGlashen ND, Cook SJ, Melrose W, et al. Maternal selenium levels and sudden infant death syndrome (SIDS). *Aust N Z J Med* 1996;26:677-682.
73. Reid GM, Tervit H. Sudden infant death syndrome and placental disorders: the thyroid-selenium link. *Med Hypotheses* 1997;48:317-324.
74. Winklhofer-Roob BM, Tiran B, Tuchschnid PE, et al. Effects of pancreatic enzyme preparations on erythrocyte glutathione peroxidase activities and plasma selenium concentrations in cystic fibrosis. *Free Radic Biol Med* 1998;25:242-249.
75. Linday LA, Dolitsky JN, Shindledecker RD, Pippenger CE. Lemon-flavored cod liver oil and a multivitamin-mineral supplement for the secondary prevention of otitis media in young children: pilot research. *Ann Otol Rhinol Laryngol* 2002;111:642-652.
76. Kalita B, Nowak P, Slimok M, et al. Selenium plasma concentration in children with celiac disease in different stages of diagnosis. *Pol Merkuriusz Lek* 2002;12:43-44. [Article in Polish]
77. Bates CJ, Thane CW, Prentice A, Delves HT. Selenium status and its correlates in a British national diet and nutrition survey: people aged 65 years and over. *J Trace Elem Med Biol* 2002;16:1-8.



78. No authors listed. Vitamins to protect against and reverse aging. *Dermatol Nurs* 2002;14:206-207.
79. Hawkes WC, Hornbostel L. Effects of dietary selenium on mood in healthy men living in a metabolic research unit. *Biol Psychiatry* 1996;39:121-128.
80. Thompson HJ, Meeker LD, Becci PJ. Effect of combined selenium and retinal acetate treatment on mammary carcinogenesis. *Cancer Res* 1981;41:1413-1416.
81. Ip C. Interaction of vitamin C and selenium supplementation in the modification of mammary carcinogenesis in rats. *J Natl Cancer Inst* 1986;77:299-303.
82. Bratter P, Negretti de Bratter VE. Influence of high dietary selenium intake on the thyroid hormone level in human serum. *J Trace Elem Med Biol* 1996;10:163-166.
83. Vinceti M, Wei ET, Malagoli C, et al. Adverse health effects of selenium in humans. *Rev Environ Health* 2001;16:233-251.
84. Standing Committee on the Scientific Evaluation of Dietary Reference. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington: National Academy Press; 2000.
85. Stahl W, van den Berg H, Arthur J, et al. Bioavailability and metabolism. *Mol Aspects Med* 2002;23:39-100.