

# SELENIUM: A QUEST FOR BETTER UNDERSTANDING

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*Selenium is an essential trace element in nutrition for the prevention of disease in humans. Epidemiological studies indicate an association between low nutritional selenium status and increased risks of cardiomyopathy, cardiovascular disease, and carcinogenesis in various sites of the body. The role of selenium supplementation in the prevention and treatment of AIDS-related pathology has been considered.*

*Selenoproteins discovered in mammalian cells may account for the essentiality of selenium in the body's antioxidant defense; thyroid hormone function; immune system function, particularly the cellular immunity; formation of sperm; and functioning of the prostate gland. The seleno-organic compounds, primarily L-(+)-selenomethionine, generally are recognized as safe and effective forms of selenium supplementation.*

*The nutritionally recommended dose of elemental selenium is estimated at 50 to 200 mg per day. There is, however, increased discussion of a pharmacological dose of selenium, significantly higher than the nutritional dose of the microelement, to treat active conditions. One way of increasing the tissue levels of selenium is to combine its ingestible form with a nutrient bioavailability enhancing compound. (Alternative Therapies in Health and Medicine. 1996;2(4):59-67)*

**T**he need for selenium as an essential trace element in nutrition for the prevention of disease was established by Schwarz and Foltz<sup>1</sup> in 1957. Selenium deficiency has been linked with a number of symptoms in animals including liver necrosis in rats,<sup>1</sup> muscular

dystrophy in sheep and calves,<sup>1</sup> pancreatic atrophy and exudative diathesis in chicks,<sup>3</sup> and liver and heart necrosis in pigs.<sup>1</sup>

Human 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>1</sup> Besides cardiomyopathy, the following clinical and/or laboratory manifestations of selenium deficiency in humans have been described: myositis,<sup>2</sup> whitening of the fingernail beds,<sup>6</sup> pseudoalbinism,<sup>7</sup> elevated creatine kinase derived from muscles, macrocytosis,<sup>7</sup> and osteoarthropathy, known as Kashin-Beck disease.<sup>1</sup>

Epidemiologic investigations in Finland, a low selenium area, indicated an association of low nutritional selenium status and increased risk of cardiovascular disease.<sup>9</sup> It also has been postulated that the unusually high mortality rate from cardiovascular disease in southeastern Georgia might be due to selenium deficiency.<sup>10</sup> The inverse association between serum selenium levels and the carcinogenesis in various sites of the body including cancers of the liver, mammary gland, esophagus, stomach, colon, rectum, lung, urinary tract, prostate, female reproductive organs, thyroid, hematologic system, oral cavity, pharynx, and skin has been noted.<sup>11</sup> The miscellaneous conditions in which the inverse association between levels of environmental selenium and the occurrence of disease has been implied include endemic goiter, sudden infant death syndrome, multiple sclerosis,<sup>12</sup> and schizophrenia.<sup>13</sup>

## ROLE OF SELENIUM IN DEVELOPMENT AND PREVENTION OF CANCER

A strong inverse correlation ( $r = -.49$ ,  $P < .05$ ) was found in a study of the relationship between average blood selenium levels and cancer mortality among persons 35 to 74 years of age in several cities in the United States.<sup>14</sup> An inverse association also was observed between selenium levels in the water and cancer mortality in Texas.<sup>15</sup> Low colorectal cancer mortality in Seneca County, NY, was observed in conjunction with high environmental selenium; conversely, high colorectal cancer mortality was found in surrounding counties with low environmental selenium.<sup>16</sup>

Correlation between average blood selenium levels in 27 countries and overall age-adjusted cancer mortality in these countries was strong and inverse for both sexes ( $r = -.7$ ,  $P < .001$ ).<sup>17</sup>

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In a study conducted in China, a significant inverse association was observed between blood selenium levels and overall age-adjusted cancer mortality ( $r=-.6$ ,  $P<.01$ ) for both sexes.<sup>18</sup> In a study conducted within one region in China, a strong inverse association was demonstrated between selenium content of grain and age-adjusted incidence of primary liver cancer." In South Africa significantly lower blood selenium levels were demonstrated in populations with high esophageal cancer incidence rates, as compared with populations with low incidence rates."

The data on the role of selenium in carcinogenesis are highly suggestive. However, the effect of selenium status and supplementation on cancer risk might depend on interactions of selenium with primary risk factors (eg, smoking history, alcohol use, age, gender, and diet)."

This aspect is illustrated by a large cohort study" in which 62,641 nurses in the United States were tested for selenium levels in toenails, after which their health status was followed for 41 months. No significant associations were observed between toenail selenium levels and cancer, including breast cancer in women." However, in a study involving 27 countries it was shown that breast cancer mortality was inversely related ( $r=-.8$ ) to yearly dietary selenium intake.<sup>17</sup>

Interestingly, it has been reported that areas of low selenium ingestion also tend to be areas of greater affluence.<sup>22</sup> The levels of environmental selenium might have an impact on the magnitude of the protective effects of the nutritional supplementation of selenium. For example, nutritional intervention with selenium in areas with low environmental selenium—like Finland—may have a greater protective effect against cancer." Conversely, populations with levels of selenium exposure above or approaching the levels at which cancer risk plateaus may not benefit from dietary selenium supplementation."

The complex interrelationship between environmental selenium, nutrition, and health is further demonstrated when one compares a selenium-deficient population of Keshan disease-endemic areas in China with a selenium-deficient population in New Zealand." In New Zealand, no direct link has been found between low selenium levels and a high risk of developing disease (other than persistent anecdotal reports from farmers that supplementation with selenium helps to relieve muscular pain and aches). According to Yahn, the difference between diets in China and New Zealand supports the idea that the nutritional interrelationships of selenium could be more important than selenium status per se.<sup>24</sup>

#### ROLE OF SELENIUM IN PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

The potential protective effect of selenium in those with AIDS has been considered both because of selenium's recognized effect against a number of viral pathogens<sup>25,27</sup> and because symptoms of impaired immune response, similar to those in AIDS, were associated in vitro and in vivo with selenium deficiency."<sup>28</sup> The nutritional status of selenium in HIV infection also has been studied."<sup>29</sup>

In one study, plasma and red blood cell levels of selenium were significantly lower than in healthy controls ( $P<.001$ ;  $P<.005$ ). No significant relationship was found between weight loss or disease duration and selenium levels." In a study of patients with AIDS and AIDS-related complex, selenium deficiency (assessed by plasma levels and red blood cell levels and glutathione peroxidase activity) was significantly related to the stage of HIV infection."

Postmortem study of selenium levels in cardiac muscle showed significantly lower levels of the trace element in AIDS cases compared with age-matched non-AIDS controls ( $P<.01$ ). The hearts of those with AIDS were histologically abnormal, and some specimens showed histological changes similar to abnormalities described in Keshan disease."

The correlation between trace elements selenium, zinc, and copper, and the serum levels of  $\beta_2$ -microglobulin was studied in 80 HIV1, seropositive patients.<sup>36</sup>  $\beta_2$ -microglobulin is considered a clinically useful marker of AIDS progression. Serum selenium levels were significantly lower in AIDS patients than in the healthy adults, whereas zinc was moderately diminished (copper values were within normal range). Negative correlations were found between zinc and  $\beta_2$ -microglobulin ( $P<.005$ ) and between selenium and  $\beta_2$ -microglobulin ( $P<.05$ ). There also was a positive correlation between selenium and zinc values ( $P<.05$ ).

In one intervention study, selenium supplementation was shown to improve AIDS-related cardiomyopathy." In another study, 12 patients with AIDS were treated with oral selenium supplements. Serum selenium levels were raised to normal with subjective clinical improvement, but no improvement or changes in hemoglobin, erythrocyte sedimentation rate, or CD4 cell counts were noted.<sup>38</sup> Studies on selenium's therapeutic role with AIDS patients show moderate improvement of their clinical status.<sup>39-41</sup>

There is general agreement that the nutritional requirement for selenium and other essential nutrients must be considered carefully in the complex therapy with which AIDS patients are treated. The effective dose of selenium required for intervention in the disease development is of particular importance. Some researchers predict that this dose is higher than the dose range required for dietary selenium supplementation."

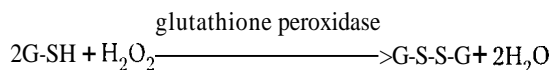
#### MECHANISM OF ACTION OF SELENIUM IN THE BODY

In the late 1950s two independent discoveries helped to elucidate the role of selenium as a necessary component of good nutrition. The first was Schwarz and Foltz's finding that selenium could prevent dietary liver necrosis, a condition that occurs in rats fed diets low in vitamin E, sulfur amino acids (cysteine, methionine), and selenium.' The second finding was that the enzyme glutathione peroxidase uses reduced glutathione to protect hemoglobin from oxidative breakdown by hydrogen peroxide.'

#### Function of Selenium in Glutathione Peroxidase

In the 1970s the findings of Rotruck and colleagues." that selenium is a crucial component of glutathione peroxidase, and

Forstrom and colleagues." that selenium is present as selenocysteine at the active site of the enzyme, helped to link these two discoveries. Glutathione peroxidase catalyzes oxidation of reduced glutathione, which reduces hydrogen peroxide and prevents lipid peroxidation and other antioxidant reactions. The reaction with hydrogen peroxide may illustrate the antioxidant mechanism of glutathione:



The oxidized glutathione formed in this reaction is converted back (regenerated) to its reduced form by a subsequent reaction with nicotinamide-adenine-dinucleotide phosphate [reduced form] (NADPH). The importance of this ox-redox reaction becomes apparent in the pathogenesis of hemolytic anemia that results from a genetically conditioned deficiency of glucose-6-phosphate dehydrogenase that reduces nicotinamide-adenine-dinucleotide phosphate in its oxidized form to NADPH. The deficiency of NADPH as a result of glucose-6-phosphate dehydrogenase deficiency prevents the conversion of glutathione to its reduced form, which can lead to the accumulation of hydrogen peroxide and destruction of erythrocytes.

Rotruck and colleagues' discovery in 1973 that selenium is an indispensable part of the enzyme glutathione peroxidase provided a rationale for the importance of selenium as an essential part of human nutrition. This discovery also provided a rationale for naming selenium as an antioxidant, because it was known that the glutathione peroxidase-dependent mechanism protects cellular components from oxidative stress and damage. Glutathione is a key compound in preventing free radical pathology. In one study, glutathione concentrations were measured in 33 people over 60 years of age, and the values were related to the self-reporting of health status, number of illnesses, and specific risk factors for chronic diseases (eg, cigarette smoking, alcohol abuse, high cholesterol, elevated blood pressure, and high body mass index)." Glutathione concentrations correlated positively with age and good health. The association with health was independent of age."

#### Selenium in Antiviral Defense: HIV, Ebola Virus, Cocksackievirus

Selenium and glutathione may also play a role in modifying HIV infection in vitro and in vivo. According to a theory proposed by Taylor and colleagues," HIV may carry several genes with the potential to encode selenoproteins, and one of these proteins may have a propensity to bind with DNA, acting as a repressor of HIV virus transcription. That mechanism could result in turning off the expression of the HIV, hence slowing the virus proliferation. This theory could explain the different clinical courses that HIV infection has taken. For example, there are known cases of HIV-positive individuals who are long-term survivors and remain asymptomatic. According to Taylor's theory, once the virus uses up the reserves of selenium in the infected

cell. the virus's repressed ability to proliferate is de-repressed and it infects adjacent cells in a "search" for the unexploited sources of selenium, thereby spreading the infection throughout the body."

The recent Ebola virus epidemic in Zaire, in which selenium-deficient regions have been documented, provides a grounding for the extension of Taylor's theory. According to Taylor the highly pathogenic Zaire strain of Ebola virus encodes a selenoprotein that would require 16 atoms of selenium per molecule. Therefore, the infection with the Zaire strain of the Ebola virus, in theory, could cause a rapid depletion of selenium in the body. It should also be noted that the selenoprotein encoding gene is absent in the Ebola Reston strain, which is considered nonvirulent in humans (Taylor EW, Ramanathan CS, unpublished data. June 1995).

The inverse association between the intracellular levels of glutathione and replication of the HIV genome, which is assessed by the activity of the transcription factor NF-KB (Nuclear Factor-kappa B), has been noted." NF-KB is a protein complex that is important in the early stages of immunological defense, because it can activate a variety of genes affecting that defense. The activity of NF-KB increases when intracellular levels of glutathione are low, which in turn leads to the increased transcription of a number of cellular genes as well as increased replication of the HIV genome." It has been postulated that oxidants may activate NF-KB.<sup>48</sup> For example, tumor necrosis factor (TNF), a cytokine that is under transcriptional control of NF-KB and promotes transcription of HIV,<sup>49</sup> also is known to induce oxidative stress, possibly by increasing the generation of superoxide anions in mitochondria.<sup>50</sup> Because addition of H<sub>2</sub>O<sub>2</sub> to the culture media can activate replication of HIV,<sup>51</sup> it is plausible to speculate on the role of an antioxidant therapy in this particular infection and in viral diseases in general.

According to one theory regarding the spreading of HIV, blood cells containing the latent virus could be triggered by reactive oxygen species released by stimulated leukocytes.<sup>52</sup> NF-KB could be stimulated by oxidative stress, subsequently binding to a specific part of the HIV genome, known as long terminal repeat, which would lead to activation of the latent provirus or activation of virus replication. This hypothesis is supported by the demonstration that antioxidant agents can prevent the chain reaction of NF-KB activation and HIV long terminal repeat transcription."

The relationship between selenium deficiency and coxsackievirus-caused myocarditis in mice has been studied." It was found that selenium-deficient mice inoculated with the benign virus produced a mutant virus with a virulent phenotype, which resulted in severe myocarditis. Animals that had adequate levels of selenium did not develop the disease. Furthermore, coxsackievirus recovered from the hearts of selenium-deficient mice and inoculated into selenium-adequate mice still induced significant damage to the heart. These data demonstrate that selenium deficiency in mice triggers phenotypic change to virulence. most likely because of point mutations in the viral genome. The

authors of this report hypothesize that the viral genome mutations in selenium-deficient animals may be a result of (1) rapid replication because of impaired immunological control, (2) lack of proofreading capability in an RNA virus and thus more likelihood of an error, and (3) increased oxidative damage to the genome resulting in sustained damage and mutation.

### Mechanism of Selenium as an Anticarcinogenic Agent

The anticarcinogenic action of selenium may or may not be mediated by its antioxidant properties or alterations in the glutathione peroxidase function. The ability of selenium with or without vitamin E supplementation to modify the chemically induced carcinogenicity and tissue peroxidation in rats was evaluated." The supplemental selenium significantly reduced the total number of mammary tumors in rats, whereas vitamin E administration was ineffective in preventing the tumor formation (as compared with the nontreated animals). However, supplemental selenium was significantly less effective than vitamin E in preventing tissue peroxidation induced by the carcinogen. Combined supplementation of selenium and vitamin E resulted in an additional decrease in the tumor incidence and degree of tissue peroxidation as compared with the experimental groups receiving only selenium or vitamin E, respectively.

These results provide evidence that the protective effects of selenium against cancer can be mediated through a mechanism other than the prevention of free radical pathology.<sup>54</sup> Nevertheless, the synergism between vitamin E and selenium may reduce the oxidative stress and facilitate selenium's anticarcinogenic properties. Another probable anticarcinogenic mechanism is the inhibition of cell proliferation by selenium.<sup>55</sup>

### Selenoproteins

Further understanding of the biological mechanism of selenium derives from discoveries in the 1980s and 1990s of proteins other than glutathione peroxidase whose structures require the presence of selenium. Some of these selenoproteins have been identified in bacteria (eg, glycine reductase in Clostridia, formate dehydrogenase in *Escherichia coli* and Salmonella, and hydrogenases in certain anaerobic bacteria)." Several selenoproteins have been isolated from mammals."

Type I iodothyronine deiodinase, an enzyme necessary for proper thyroid function and conversion of thyroxine ( $T_4$ ) into triiodothyronine ( $T_3$ ), is a selenoprotein containing selenium in the form of selenocysteine.<sup>57</sup> The messenger RNA for this enzyme contains a codon for incorporation of selenocysteine."

The results of clinical evaluation of the role of selenium in thyroid function are equivocal. In one study of healthy schoolchildren from northern Zaire, Africa, where goiter is endemic and selenium deficiency is prevalent, selenium supplementation corrected the low levels of serum selenium and red blood cell glutathione peroxidase activity. Supplementation of selenium in this study decreased serum levels of  $T_4$  without affecting the levels of  $T_3$ , thyroid stimulating hormone, and thyroxine-binding globulin.<sup>58</sup> However, supplementation of selenium in those with

severe impairment of thyroid function in northern Zaire resulted in a significant decrease in serum levels of  $T_4$ , with a significant increase in levels of thyroid stimulating hormone."

In view of these results, selenium supplementation, particularly in areas in which goiter is endemic, should be carefully considered, and possibly combined with iodine supplementation. These results also show that the relationship between selenium and iodine has yet to be understood. A link between iodine deficiency and selenium deficiency has been postulated in sudden infant death syndrome, breast cancer, and multiple sclerosis."

A new form of glutathione peroxidase containing selenocysteine, called phospholipid hydroperoxide glutathione peroxidase, has been described in porcine heart and liver." This enzyme differs from classical glutathione peroxidase in terms of its target of antioxidant activity; it specifically reduces lipid peroxides in cell membranes.

Selenoprotein P is another selenocysteine that contains protein isolated from rat plasma." The plasma concentrations of selenoprotein P are very sensitive to levels of dietary selenium. This protein was the first to incorporate labeled selenium administered to rats." It has been postulated that selenoprotein P may be involved in selenium transport as well as in the prevention of free radical pathology.<sup>61,62</sup>

The major structural protein of mouse sperm mitochondria was identified as a selenoprotein.<sup>63</sup> This selenoprotein is responsible for shaping mitochondria into the helical sheath that surrounds the flagellum, in accordance with the role of mitochondria in assisting sperm motility.

Selenoprotein W was isolated from the skeletal muscle of a rat.<sup>64</sup> The importance of this mammalian selenoprotein should be considered in view of a selenium-responsive myopathy in lambs and calves.<sup>2,64</sup>

Another important addition to the family of selenoproteins is a cytosolic selenoprotein found in rat prostate." The potential importance of this selenoprotein stems from epidemiological studies that show an inverse relationship between the status of selenium and the incidence of prostate cancer, and from experimental results showing that selenium is preferentially incorporated into this compound rather than another selenoprotein, glutathione peroxidase." Evidence also indicates that selenoproteins may be encoded in the human genes responsible for the expression and regulation of cellular immunity."<sup>65</sup>

### Possible Role of Selenium in Blood Coagulation and as an Antiarrhythmic Agent

Some findings concerning the role of selenium in modifying the body's homeostasis relate to its effect on blood coagulation and its potential as an antiarrhythmic agent." Selenium deficiency in rats significantly decreased aortic prostacyclin synthesis, but did not affect the platelet thromboxane synthesis. The results of this experiment indicate that selenium may play a role in inhibiting blood clotting. The potential effect of selenium on blood coagulation was demonstrated in a report from China, where 80 patients with cases of epidemic hemorrhagic fever were

treated with multiple doses of 2 mg/d selenite in the first 9 days of hospitalization.<sup>88</sup> As a result of the therapy the mortality dropped significantly, as compared with the patients who received only conventional, life-supporting treatment. The laboratory data indicated that the therapeutic benefit might be due to the inhibition of complement activation in the group receiving selenium treatment.

Selenium supplementation is increasingly considered to be an adjuvant or a sole treatment modality of cardiac arrhythmias. In one report ventricular tachycardia resistant to several standard therapeutic agents was normalized after selenium supplementation to the patient.<sup>89</sup>

### Hypothetical Role of Selenoprotein P in Psychiatric and Mood Disorders

Selenoprotein P was discussed in a hypothetical model in which the defect of selenium transport protein, resulting in low levels of selenium at the tissue level, may play a role in pathogenesis of schizophrenia.<sup>90</sup> In that model six biochemical markers associated with selenium deficiency were correlated with schizophrenia: n-6 essential fatty acids reduced and n-3 essential fatty acids elevated, decreased levels of prostaglandins E and F, low levels of glutathione peroxidase, reduced conversion of thyroid hormone T<sub>4</sub> to T<sub>3</sub>, low levels of erythrocyte ubiquinone-10, and increased levels of phospholipids (particularly sphingomyelin).

Based on a report originating in the US Department of Agriculture, it has been suggested that providing supplemental selenium to a group of men (total daily dose of approximately 200 µg) resulted in the improvement of their moods. The men felt more relaxed, less confused, less anxious, and more confident and energetic. Participants with the lowest mood at the beginning of the study benefited most from selenium supplementation (*Newark Star-Ledger*, Newark, NJ; September 13, 1995:42).

### SAFETY AND EFFICACY OF SELENIUM SUPPLEMENTATION

The bioavailability, efficacy, and ultimately the safety of selenium supplementation may depend on a number of factors including the amount of selenium in the diet, its chemical form, its interaction with other nutrients, and the physiological state of the host.<sup>91</sup>

As a member of the sulfur family of elements, selenium shares some chemical properties with sulfur, including valency states and the ability to form covalent bonds with carbon.<sup>92</sup>

L-(+)-selenomethionine is readily absorbed from the gastrointestinal tract.<sup>93</sup> It is significantly better absorbed and retained in the body than inorganic selenium in the form of selenite.<sup>93</sup> L-(+)-selenomethionine has slower whole-body turnover compared with selenite—an attribute that provides efficient use of the selenium contained in complex with methionine.<sup>94</sup>

In another study, human milk supplemented with selenomethionine resulted in higher plasma selenium concentrations in infants than did those obtained from supplementation

with selenium-enriched yeast.<sup>95</sup>

Dietary supplementation with selenomethionine, selenite, and selenocysteine in rats showed that the highest increase in tissue selenium levels was accomplished with selenomethionine.<sup>95</sup> The tissue selenium increase with selenomethionine compared with other forms of selenium tested was most significant in muscles.<sup>95</sup>

Interaction between selenium and other dietary constituents may affect the biological properties of selenium. For example, supplements of selenium with vitamin A may provide an added protective effect against breast cancer.<sup>96</sup> It also has been found that there is a strong inverse association between selenium levels and cancer risk in persons with low levels of serum α-tocopherol, serum beta carotene, and serum retinol.<sup>97,98</sup>

Unfortunately, vitamin C may have the opposite influence on the biological protection offered by some forms of selenium. In one experiment, selenomethionine and selenite when used alone were equally effective against chemically induced mammary carcinoma in rats.<sup>99</sup> The protective effect of selenite was nullified by supplementation with vitamin C; the protective effect of selenomethionine, however, was not affected by vitamin C.

The negative feedback between selenite and vitamin C supplementation was dose dependent and was not produced with low levels of vitamin C.<sup>90</sup> It has been postulated that selenite is reduced by vitamin C to elemental selenium and is therefore poorly bioavailable.<sup>91</sup> Glutathione may also play a role in the interaction between selenite and vitamin C, because glutathione oxidation may be an important intracellular mechanism of vitamin C regeneration.<sup>100</sup>

An important aspect of selenium supplementation is its potential toxicity. In fact, selenium belongs to the vast group of therapeutics that can be "villains" or "heroes" depending on the way they are used. Indeed, early research on the role of selenium in the diet focused on toxic effects at high doses.<sup>101</sup>

Seleno-organic compounds, like selenomethionine, generally are recognized as less toxic than inorganic forms of selenium such as selenite. The role of methionine in aiding the safe metabolism of selenium is part of that safety mechanism.<sup>83</sup> The biological effectiveness of seleno-organic compounds vs inorganic selenium is the subject of scientific discussion at present. In view of the apparent efficacy of both forms of selenium, preference is given to the safety and efficacy offered by seleno-organic compounds.<sup>102</sup>

The role of safer seleno-organic compounds should not be minimized, because selenium may have toxic effects at levels only four to five times that normally ingested in the human diet (Agency for Toxic Substances and Disease Registry: 1989). An increasing body of evidence, however, supports the notion that the health benefits of selenium supplementation can be accomplished at much higher doses than the currently recommended 50 to 100 µg/d elemental selenium supplementation. For example, the long-term study of 113 persons in China who received 200 µg elemental selenium in the form of an organic compound for 3 years showed significantly lower incidence of primary liver cancer than did the placebo group.<sup>103</sup> According to some

researchers, the recommended daily dose of selenium could be as high as 200 to 300  $\mu\text{g}$ .<sup>85</sup> According to Passwater, some populations ingest 600 to 700  $\mu\text{g}/\text{d}$  elemental selenium and have good health without adverse reactions.<sup>85</sup>

As mentioned, an important distinction should be made between the dose of supplemental selenium and the increasingly discussed pharmacological dose of selenium, particularly in cases of viral agents like HIV and Ebola virus. For example, the Chinese used multiple doses of 2 mg selenite daily in a successful attempt to reduce mortality due to epidemic hemorrhagic fever.<sup>86</sup> The antiarrhythmic and myocardium protective dose of selenite evaluated in experimental animals was 1 to 2 mg/kg body weight administered intravenously.<sup>86</sup>

One of the proposed solutions to the dilemma of higher doses of selenium required for its biological activity is increasing its bioavailability, or maximizing its presence in the target tissue. The bioavailability of selenium was evaluated in a double-blind study with 10 volunteers, 5 of whom received 50  $\mu\text{g}$  elemental selenium in the form of L-(+)-selenomethionine alone, and 5 of whom received 50  $\mu\text{g}$  elemental selenium in the form of L-(+)-selenomethionine supplemented with a small amount of naturally derived pure alkaloid piperine in the form of a preparation known as Bioperine<sup>®</sup>. Over the course of a 6-week supplementation regimen, serum selenium levels were evaluated before the study and at 2-, 3-, and 6-week intervals. The serum selenium levels were approximately 30% higher in the group receiving selenium with Bioperine. This increase was detected after 2 weeks of supplementation, with a plateau in the subsequent time-points tested. None of the volunteers in the experimental groups reported any adverse effects from the supplementation. The serum selenium levels were within normal limits in both groups at all time-points tested. These preliminary results, reported for the first time in this article, may indicate that the bioavailability of selenium can be safely increased.

## CONCLUSION

Because the essentiality of selenium for human nutrition is well established, a more intelligent use of this compound in the prevention and treatment of human pathology is at stake now. The role of selenium in human health may be increasingly important because selenium deficiency in the food chain is well recognized. Selenium deficiency poses a serious problem in livestock worldwide, which ultimately may affect the selenium status in humans.<sup>87</sup> It is therefore important to address selenium's nutritional and therapeutic role with a sense of urgency. This, however, should be done according to the old medical axiom of *primum non nocere*: know what you are doing to avoid hurting the patient.

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