

REPORT

Getting Serious about Selenium

By Dale Kiefer



The trace element selenium was once thought to be nothing more than a curiosity. Chemically similar to sulfur, which has known biological functions, and found in soils throughout much of the world, selenium was nevertheless considered biologically irrelevant.

By the mid-twentieth century, however, scientists had discovered that selenium is an essential nutrient for animals. Without it, they realized, animals cannot function properly.^{1,2}

Entering the twenty-first century, we now know that selenium is crucial to the health of humans and animals alike. Moreover, in the nutritional sphere, selenium is considered a rising star that offers protection against a wide range of damaging diseases and conditions.

Selenium's promotion from irrelevant mineral to essential trace element is the result of our growing understanding of its multifaceted, indispensable roles in regulating metabolism, orchestrating normal growth, launching successful reproductive efforts, neutralizing free radicals, and defending the body against infections, among other key life processes.³

In fact, selenium is so important to the human body that it is the only essential trace element specified in the genetic code. Selenocysteine, known as the twenty-first amino acid, is incorporated in numerous proteins under the direction of human genetic code.⁴ Although plants do not appear to require selenium, many plants extract it from soil and store it in their tissues, where it is available for consumption by humans and animals.^{1,2}

In the early 1970s, scientists discovered that selenium plays an integral role in protecting human cellular membranes from peroxide damage, by virtue of its inclusion in glutathione peroxidase, a natural antioxidant enzyme. Today, we know that selenium is incorporated in at least 25 unique proteins in the body. Known as selenoproteins, they play integral roles in everything from activating thyroid hormone and regenerating spent vitamin C, to promoting healthy pregnancies.⁵⁻⁸



Selenium's Multiple Roles

Scientists have identified four different glutathione peroxidases containing selenium.³ In their crucial role as antioxidant enzymes, each of these distinct proteins neutralizes potentially damaging free radicals, or reactive oxygen species, by removing oxygen molecules and thus transforming the threatening compounds into harmless molecules such as water or alcohols. Their targets include destructive hydrogen peroxide and lipid hydroperoxides.

Another selenium complex, known as selenoprotein P, circulates in blood plasma and is associated with cells lining the interior of blood vessels. Although selenoprotein P's functions remain sketchy, it is believed to protect blood vessels by neutralizing the reactive oxygen

species peroxynitrate, and to act as a transport protein.^{5,9,10}

Key to Thyroid Hormone Regulation

Still other selenium-containing proteins, the iodothyronine deiodinases, are responsible for making active thyroid hormone available in the general circulation. Indeed, the thyroid gland holds the highest selenium concentration of any organ in the body, due to selenium's crucial role in transforming inactive thyroxine, or T4, into biologically active thyroid hormone (triiodothyronine, or T3), by catalyzing the removal of iodine from T4. Three different selenium-containing enzymes are responsible for both activation and inactivation of thyroid hormone.

Selenium is essential, therefore, to the success of important processes regulated by thyroid hormone, such as normal growth, development, and metabolism.¹¹ Scientists recently examined selenium status and thyroid health among 1,900 people in France in a large, ongoing study of nutritional status and health. They determined that selenium may offer significant protection against the development of goiter and other abnormalities



of the thyroid gland, particularly when iodine levels are low.¹²

Supporting Healthy Immune Response

Selenium is a crucial component of a properly functioning immune system. In recent years, scientists have discovered that selenium deficiency allows an otherwise benign virus, coxsackievirus, to mutate into a vicious microbe capable of attacking heart muscle. A heart condition known as Keshan disease is widespread in certain areas of rural China, where the soil is poor in selenium and people subsist on locally grown food. In these areas, adult life spans have been shortened and children in the most selenium-deficient areas have been reported to succumb to the fatal disease at 1 to 10 years of age.¹³ Selenium supplementation is known to protect against development of Keshan disease.^{1,2}

Scientists recently have shown that selenium deficiency is directly related to the development of Keshan disease in a mouse model.¹⁴⁻¹⁷ It is highly likely that selenium plays a similar role in protecting humans against the viral mutation associated with the development of Keshan disease. In a related finding, scientists have discovered that selenium deficiency in mice is also associated with greater virulence of an otherwise mild strain of the influenza virus. Mice deprived of selenium experienced far worse inflammation of the lungs because of influenza infection than control mice receiving selenium in their diet. Lack of selenium promoted changes in the genetic material of the virus, allowing it to become more dangerous.¹⁵⁻¹⁸

This link between selenium deficiency and increased viral virulence is suspected to underlie several other diseases. Researchers in China have shown that supplementation with selenium dramatically reduces the incidence of hepatitis B viral infection in both animals and humans. In those already infected, supplementation significantly prevented progression of the infection to deadly liver cancer. When supplementation was withdrawn, liver cancer rates began climbing to previous levels.¹⁹

In numerous recent medical journal reports, researchers have noted the importance of selenium in preventing progression of HIV infection to full-blown AIDS.^{1,20-22} HIV-positive men and women receiving selenium supplementation were admitted to the hospital less often than HIV-positive patients receiving placebo, according to the results of a placebo-controlled, double-blind study conducted in Florida. As reported recently in the medical journal *HIV Clinical Trials*, researchers found that overall hospitalization costs dropped 28% among patients receiving selenium therapy compared to those receiving the placebo supplement.²²



Selenium Deficiency Tied to Deadly Viruses

Scientists have long known that malnutrition is associated with a higher incidence of infection and disease. It was assumed that this susceptibility to illness results when an immune system weakened by nutritional deficiencies becomes incapable of mounting an adequate defense. However, new findings about selenium have prompted a dramatic shift in our understanding of infection and disease. As a direct result of selenium-deficiency research, we now know that malnutrition not only weakens the immune system, but also, in some instances, transforms the pathogens that seek to infect us, rendering them more destructive.

Once the pathogen's genome has changed, subsequent progeny of that pathogen retain the newfound level of virulence; that is, they are capable of infecting even healthy individuals whose selenium levels are optimal.^{3,15} In essence, if you are selenium deficient, you could become a sort

of viral incubator, capable of producing far more dangerous pathogens that endanger not only your health but that of your neighbor.

This amazing discovery has led to speculation that selenium deficiency, among other vitamin and mineral deficiencies, may be responsible for the emergence of devastating viral diseases. Some scientists have even proposed that the emergence of new strains of influenza, the common cold, or even the dreaded Ebola virus may be related to viral changes wrought by interactions with selenium-deficient hosts in areas of the world (such as regions of Africa and China) where the soil's selenium content is exceptionally low.^{1,16}

Pioneering Research Melds Nutrition, Virology

Dr. Orville A. Levander is a nutritional researcher with the United States Department of Agriculture's Beltsville Human Nutritional Research Center in Maryland. For the past decade, he has collaborated with Dr. Melinda A. Beck, a leading virologist affiliated with the University of North Carolina at Chapel Hill. Together, they have investigated selenium's role in enhancing viral virulence around the world and have published their work in leading medical journals.^{15,17,23} As far as they know, their discovery that selenium deficiency promotes changes in the basic genetic material of viruses had never before been reported or even suspected, according to Levander.

“It was such an unusual twist, it almost seemed unlikely,” says Levander. “I’ll be the first to admit we didn’t expect it.” Ordinarily, Levander adds, there’s “too big a gulf” between nutritionists and virologists for successful collaboration. His work with Dr. Beck, therefore, represents a small triumph for basic medical research. “[Our work] shows the value of interdisciplinary research,” says Levander. “You get to find something quite interesting. That’s what happened to us, I think.”



Beck, Levander, and their colleagues are evidently the first scientists in history to prove that a nutritional deficiency promotes the development of more dangerous microbes. Levander is somewhat surprised that this discovery has not made a bigger splash among virologists, or among the general public, for that matter. Given the profound implications of the research, one might expect that virologists would rush to replicate and expand on their work. But that has not happened to any great degree, says Levander. He speculates that scientists’ specialization and narrow focus may be the reason. In the meantime, he notes that the National Cancer Institute is funding a large clinical trial designed to show definitively whether selenium protects against cancer. In about three years, when those results become available, Levander predicts, “All hell may break loose.”

As one scientist has declared, the bottom line regarding our current understanding of selenium’s role in immunity is this: “Selenium supplementation appears to enhance the immune response.”¹ Even in individuals with “normal” levels of selenium, supplementation has been shown to stimulate the immune system, provoking a proliferation of activated T cells. Human lymphocytes showed an increased ability to transform into cells capable of destroying tumor cells, and natural killer cell activity increased by 82% above baseline activity after supplementation with 200 micrograms (mcg) per day of selenium.²⁴ In subsequent work, the same research team discovered that selenium supplementation “restores age-related decline in immune cell function.”²⁵

Selenium Is Cancer Preventive

Some of the most exciting selenium research currently under way involves the nutrient’s ability to prevent cancer. Selenium gained national attention in the mid-1990s, with the release of findings from the Nutritional Prevention of Cancer (NPC) study conducted by researchers at the University of Arizona. More than 1,300 skin-cancer patients from clinics across the eastern US were assigned to receive either 200 mcg of selenium per day or placebo. Researchers wondered whether selenium could protect subjects from repeat bouts with basal cell or squamous cell carcinoma, which ordinarily recurs in about 25% of cases. Participants were treated for an average of four and a half years, with about six and a half years of follow-up. Although the incidence of repeat skin cancers was not reduced among selenium patients, the selenium group did experience 46% fewer lung cancers, 58% fewer colorectal cancers, and a remarkable 63% fewer prostate cancers than patients in the placebo group. In all, the selenium group recorded 50% fewer cancer deaths than the placebo group.²⁶⁻²⁸

Researcher GF Combs Jr., who was involved with the investigation from its inception, told Life Extension: “When we started planning this, I was skeptical. I didn’t expect us to find anything of significance. Our formal hypothesis was that selenium would have no effect on cancer rates.” But blinded data soon revealed that one group of patients was experiencing a lower overall death rate. “One parameter we looked at was survival rates,” says Dr. Combs. A safety review committee mandated the implementation of secondary end points. Without changing the study’s initial design, researchers would now document all deaths and incidences of cancer of any type among study participants. That analysis revealed the remarkable preventive effects of selenium against prostate, lung, and colorectal cancers. “I was surprised at the magnitude of the effect,” says Dr. Combs, “and I was pleasantly surprised at the consistency of the effect.”

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Is More Selenium Better?

Dr. Clark has written that selenium intake greater than that required to correct a selenium deficit may be needed to achieve this effect. In other words, meeting the US adult recommended dietary allowance (RDA) of 55 mcg per day is probably insufficient to achieve full cancer-preventive benefits. Dr. Combs points out that selenium appears to be anti-tumorigenic at levels that are “substantially greater than those associated with maximal expression of the known SeCys-containing enzymes.”

The RDA is based on the amount of selenium required to adequately produce the glutathione peroxidases (which, you will recall, require selenium), but it does not account for the potential benefits of selenium in excess of the bare minimum required to manufacture the antioxidant glutathione peroxidase enzymes. “Even individuals with nutritionally adequate selenium intakes may benefit from selenium supplementation,” writes Dr. Combs.²⁹

In a subsequent journal article, he reiterated this concern. “The findings of [Dr. LC Clark and colleagues (including Dr. Combs), published in the Journal of the American Medical Association (JAMA), in 1996]²⁸ suggest that selenium intakes of approximately twice the levels of the new [RDA], or more, can have such beneficial health effects.”³⁰

While Dr. Combs does not advocate changing the RDA at this time, he admits, “It’s a murky area. I think it’s one we’re going to be revisiting.” The RDA provides a guideline to the average daily dietary intake level that is sufficient to meet the nutritional needs of the majority of healthy individuals. However, in recognition of the fact that some nutrients may offer additional benefits at higher levels, tables of tolerable upper-intake levels (UL) were also created. The UL reflects the maximum daily intake of a given nutrient that is considered safe. For selenium, the UL for adult men and women is 400 mcg per day.³¹



In a majority of studies examining selenium’s effects on disease in humans, daily doses of 200 mcg of supplemental selenium were used. Although the National Health and Nutrition Examination Survey (NHANES III, from 1988 to 1994) determined that the diets of most Americans provide enough selenium to meet recommended amounts of the essential nutrient,³² supra-nutritional amounts may be necessary to achieve cancer prevention.³ As Dr. Combs points out, “It’s safe to take up to 200 mcg per day of selenium.”

Dr. Combs is now affiliated with the USDA’s Agricultural Research Service. Earlier this year, he published an article in the British Journal of Cancer that further elucidated the findings of the NPC trial. “Selenium treatment can promote [programmed suicide] in prostate cancer cells, and possibly, impair their proliferation through antiangiogenic effects,” wrote Dr. Combs. He noted that risk reductions were most dramatic among men entering the trial with the lowest levels of selenium.³³

Another paper published last summer reviewed research conducted in seven countries, and concluded that gender may influence selenium’s cancer-preventive effects. “Available data support the hypothesis that cancer risk in men is more profoundly influenced by selenium status than cancer risk in women,” wrote the Indiana-based researchers. They noted the need for still more research into selenium’s benefits.³⁴

A preponderance of evidence indicates that high-dose selenium supplementation reduces the incidence of cancer in animals. Of more than 100 published studies on more than 20 animal models of cancer (including spontaneous and virally and chemically induced cancers), more than two thirds found evidence of significant reductions in tumor incidence with selenium supplementation. Furthermore, it appears that methylated forms of selenium—which are produced in the highest amounts in the body when there is excess selenium intake—are the active compounds offering cancer chemoprevention.³⁵

Gastrointestinal disorders such as Crohn’s disease may interfere with nutrient absorption, resulting in trace-mineral deficiencies, but it is estimated that otherwise healthy Americans consume, on average, about 130 mcg per day of selenium. Men tend to ingest slightly more selenium than women.³⁶ Smoking is associated with a reduction in plasma selenium. People living in the South and Northeast have somewhat lower dietary intakes of selenium, due to differences in selenium concentrations in the soil (and thus food) in those regions.³⁷ The RDA of selenium for women who are pregnant or breast feeding is greater than the 55 mcg per day recommended for other adults, due to the need to provide adequate selenium for the developing fetus and to nourish the newborn with immunity-boosting selenoproteins.³¹ In fact, studies have shown that adequate selenium content in breast milk is directly related to the healthy development of the breast-feeding infant’s immune system.^{38,39}



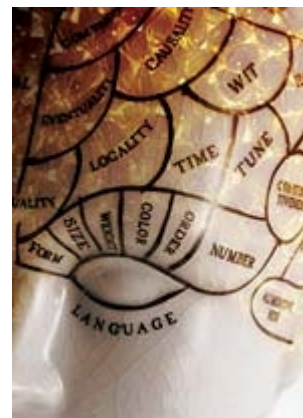
Indispensable to Brain Health

Some of the most intriguing selenium research concerns selenium's critical importance to brain health. At least three published studies have linked selenium deficiency to undesirable mood states, and several studies indicate selenium's importance to normal brain function. When individuals are selenium deprived, even for long periods, the brain hoards available selenium,⁴⁰ and the turnover rate of some neurotransmitters is affected.⁴¹ Studies have found a significant association between low selenium levels and rapid cognitive decline in the elderly.^{40,42} When the brains of Alzheimer's patients were examined for selenium status, they contained only 60% as much of this essential nutrient as the brains of control patients.⁴⁰

Since the brain is deficient in an enzyme responsible for removing damaging peroxidation products such as hydrogen peroxide, selenium-based antioxidant proteins must shoulder the job alone.⁴³ Many studies show that when selenium status is marginal, supplementation improves mood. Three separate studies have correlated low selenium status with a greater incidence of depression, anxiety, hostility, or confusion.^{40,44-46}

A report published recently in the *Journal of Nutrition* implicates selenoprotein P as a key player in brain biochemistry. Deletion of the selenoprotein P gene in genetically altered mice has been associated with neurological dysfunction and decreased brain levels of selenium.⁴⁷ Selenoprotein P acts as an antioxidant in the brain, and possesses the ability to promote neuronal cell survival.⁴⁸

It is interesting to note that alterations in selenium concentration have been reported in the blood and brains of Alzheimer's patients.⁴⁸ As another recent scientific paper notes, most of the 25 known selenoproteins can be found in the brain, but their individual contributions to brain health and function remain to be elucidated.⁴⁹ In any event, it is clear that selenium is indispensable to normal brain function.^{47,50}



Uncertain Effects on Heart Health

Although it is well established that selenium exhibits both antioxidant and anti-inflammatory properties in the body, it remains unclear whether it directly affects cardiovascular health. Given that glutathione peroxidase combats lipid oxidation and reduces platelet aggregation—which reduces clot formation and thus decreases the risk of stroke or heart attack—it seems likely that selenium will eventually prove to be cardioprotective.^{3,51} Much work remains to be done in this area of inquiry, however.⁵² As leading selenium researcher Margaret P. Rayman has written: “Any condition associated with increased oxidative stress or inflammation might be expected to be influenced by selenium status. There is some evidence that this is the case in rheumatoid arthritis, pancreatitis, asthma, and systemic inflammatory response syndrome.”³

A Final Caution

Excessive selenium intake results in the rare condition known as selenosis, characterized by garlic-scented breath, brittle hair and nails, and neurological disorders. It is unwise, therefore, to exceed the recommended daily supplemental dose of 200-400 mcg of selenium. It also bears mentioning that among food sources of selenium, only Brazil nuts represent a potentially concentrated source, which varies depending on selenium content in the soil where the nuts were grown. The National Institutes of Health's Office of Dietary Supplements estimates that one ounce of Brazil nuts contains, on average, 544 mcg of selenium. By contrast, the next most concentrated common food source—oil-packed light canned tuna—provides just 63 mcg of selenium in a three-ounce serving. Therefore, if you supplement with selenium, it may be wise to consume Brazil nuts only occasionally.

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