Articles

Selenium
Nutritional, Toxicologic, and Clinical Aspects

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This is one of a series of articles from western state public health departments.

Despite the recent findings of environmental contamination, selenium toxicosis in humans is exceedingly rare in the United States, with the few known cases resulting from industrial accidents and an episode involving the ingestion of superpotent selenium supplements. Chronic selenosis is essentially unheard of in this country because of the typical diversity of the American diet. Nonetheless, because of the growing public interest in selenium as a dietary supplement and the occurrence of environmental selenium contamination, medical practitioners should be familiar with the nutritional, toxicologic, and clinical aspects of this trace element.

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Since the recognition of the nutritional essentiality of selenium (Se) in animals in 1957, there has been ever-increasing interest in this trace element. This interest has heightened in the past decade concomitant with the recognition of selenium's essential nutritional role in humans and reports of selenium toxicity among humans. Interest in selenium has been further aroused recently by the findings of elevated levels of this compound in certain soils and water sources in the western United States, leading to adverse effects on fish and wildlife (T. Harris, "Toxic Chemicals Threaten West," *The Sacramento Bee,* September 8, 1985, pp A1, A16-A18, A20).[1,2]

Selenium occurs naturally in various types of soil and can leach into agricultural drain water. This has occurred in the San Joaquin Valley of California, where evaporation pond drain water containing elevated levels of selenium has been associated with adverse reproductive and other effects in aquatic birds at the Kesterson National Wildlife Refuge.[2] Similarly, in California's Salton Sea, Grassland Water District, Tulare Lake Basin, and Suisun Bay, elevated levels of selenium have been found in fish and aquatic birds, necessitating the issuance of health advisories by the California Department of Health Services—that is, recommendations to restrict the consumption of fish and game birds from these areas. Selenium-rich sediments also have been reported in wildlife refuges in Arizona, New Mexico, Utah, Montana, Idaho, and South Dakota (T. Harris, *The Sacramento Bee,* Sep 8, 1985). These findings have caused concern among health and wildlife personnel, as well as the agriculture industry, and have been widely reported in the media, at times causing considerable alarm among the public. Conversely, exaggerated claims about the health benefits of selenium have been made in the popular press. In this article we review the nutritional, toxicologic, and clinical aspects of selenium in an effort to assist physicians with questions and concerns about this compound.

Occurrence

Selenium is a naturally occurring element found in rock, shale, sandstone, limestone, coal, soil, surface water, and vegetation.[3] It occurs in relatively high concentrations in many of the soils of the US, especially the western states, and other parts of the world.[4] Highly seleniferous soils yielding selenium-toxic plants (such as *Astragalus bisulcatus)* are widespread in South Dakota, Wyoming, Montana, North Dakota, Nebraska, Kansas, Colorado, Utah, Arizona, and New Mexico. Soil containing high selenium concentrations but not yielding toxic plants is found in Hawaii.

Chemical Forms

Selenium is a nonmetallic element chemically related to sulfur. It occurs naturally in four oxidation states: elemental selenium, selenite, selenide, and selenate.[3] The valence state affects selenium's toxicity and bioavailability.

Industrial and Commercial Uses

Selenium is used in semiconductor research (aluminum, bismuth, and indium selenide), in the manufacture of glass (ammonium selenite, arsenic hemiselenide), in photoconductors, semiconductors, photoelectric cells, and rectifiers (cadmium selenide), and in electron emitters (calcium selenide); as a catalyst in Kjeldahl digestions (cupric selenide), as a chemical reagent (potassium selenate), in veterinarian remedies for eczemas and fungal infections, and as an antidandruff agent in shampoos for human use (selenium disulfide); in the manufacture of other selenium compounds, and as a reagent for alkaloids (selenium dioxide); and as a veterinary therapeutic agent (sodium selenate, sodium selenite).[5] Radioactive nucleotides of selenium are used as biologic tracers in radiologic diagnostic procedures—selenocysteine Se 75 and selenomethionine Se 75 are used for pancreatic imaging. Selenium is also used as a dietary supplement for some farm animals (sodium selenite), and it is taken as a nutritional supplement by humans (mostly selenium-enriched yeast products). Based on data available to the California Department of Health Services, we estimate that more than 250,000 Californians take selenium as a nutritional supplement.

Environmental Sources of Selenium Exposure

Water

Selenium, in the forms of selenite and selenate, is found in water, principally as a result of leaching from seleniferous rocks and soils.[5] At pH 6.3 to 6.7, precipitation of insoluble

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ferric selenite occurs in the presence of iron. At pH 8, it is oxidized to soluble selenate. The federal and state maximum contaminant level established for selenium in drinking water is 10 parts per billion. Water is generally not a biologically significant source of intake.

Food

The concentration of selenium in plant tissues depends on the concentration and availability of selenium in the soil where the plants are grown. Selenium-accumulator plants grow only in soil containing high levels of selenium—1 to 50 parts per million (ppm)—and accumulate concentrations of as much as 1,000 to 10,000 mg per kg.[5]

Selenium is generally found at levels of less than 1 ppm in food, wet weight. The major dietary sources of human intake are meat, poultry, grain and grain products, and seafood. The dietary selenium intake for the US population has been estimated to be in the range of 60 to 216 μg per adult person per day.[6] A daily intake of 50 to 200 μg of selenium for adults is considered adequate and safe by the Food and Nutrition Board of the National Academy of Sciences.[7] Lower intake levels are recommended for children younger than 7 years.

Air

Most urban areas have atmospheric particulate selenium concentrations ranging from 0.1 to 10 ng per m^3, contributing a biologically insignificant exposure. The occupational threshold limit value for inorganic selenium is 0.2 mg per m^3.[8]

Toxicity

Animals

The toxicity of selenium has been recognized since the 1930s when it was discovered that certain seleniferous soils produced plants having a high selenium content.[3,9] A few species of selenium-accumulator plants characteristically accumulate extremely high levels of selenium in the form of nonprotein selenoamino acids such as Se-methylselenocysteine and can cause acute toxic reactions in animals consuming them. For example, a subacute selenosis called "blind staggers" occurs in livestock feeding on plants containing 100 to 10,000 ppm selenium.[5] This disease is characterized by anorexia, emaciation, neurologic deterioration—blindness, ataxia, and disorientation—and respiratory distress. Generalized paralysis occurs in the final stages of this disease, with death being due to respiratory failure. Likewise, an alkali disease is a chronic form of selenium poisoning among livestock, caused by consuming plants containing 20 to 50 ppm selenium.[5] The major signs of this condition are emaciation and dermatologic changes, such as alopecia and hoof necrosis.[10]

Selenium poisoning has been produced in laboratory animals using various routes of administration.[8,9] Acute toxic exposure causes respiratory distress, pulmonary edema, diarrhea, hemorrhage, and liver and kidney necrosis. Chronic toxic exposure results in gastroenteritis, myocardial injury, pulmonary edema, hydrothorax, renal and liver damage, and, ultimately, death.

The dose of ingested selenium that can cause selenium poisoning depends on the chemical form of selenium, the presence of other dietary components, and the duration of ingesting selenium-rich foodstuffs. In general, chronic selenium poisoning, as manifested by anemia and hepatic necrosis, has occurred in rats and dogs fed diets containing 5 to 15 ppm selenium per day for weeks or months.[8,9] Diets containing 4 to 5 ppm per day have been shown to inhibit the growth of animals, and lower levels can be toxic if the diet is deficient in vitamin E. Similarly, caries formation may be increased if lower levels of selenium are consumed during the development of teeth.

Humans

Toxicity from acute inhalation or dermal contact. Acute human selenium toxicosis has been reported from industrial and other accidental exposures.[10] For example, inhaling selenium fumes, selenium dioxide, or hydrogen selenide causes intense irritation of the mucous membranes of the eyes and upper respiratory tract, producing ophthalmorrhea and ophthalmodynia, coryza, hoarseness, coughing, and sneezing.[7,10] Headache, dizziness, dyspnea, fatigue, nausea, vomiting, a bitter taste in the mouth, and a garlic odor of the breath may also characterize acute inhalational selenosis.

Skin exposure to selenium may cause severe local irritation, producing painful burning, erythema, and occasionally allergic dermatitis. The severity of response depends on the chemical form of the selenium compound. The most severe responses occur after exposure to the highly poisonous hydrogen selenide. Reactions to selenium oxychloride, dioxide, and hexafluoride are less severe. Elemental selenium and selenium sulfides are generally considered nontoxic.

Ingestion. A number of instances of acute selenosis from the ingestion of selenium-containing products or foodstuff have occurred in recent years (Table 1).[12-16] Illustrative of these situations was a case in New Zealand of acute selenosis from ingesting sheep drench containing 22.3 mg Se per kilogram as sodium selenate.[11] In this case, a young girl ingested 1,160 mg of selenium. Her initial serum selenium concentration was 3,100 μg per liter, and the initial 24-hour urine collection showed 680 μg per ml. She had a strong garlic odor to her breath and frequent loose, grey bowel movements. She was treated with gastric lavage, diuresis, and the administration of vitamin C and dimercaprol. She suffered no apparent sequelae, although biochemical tests suggested mild liver damage and electrocardiograms indicated a transient cardiac arrhythmia. She remained well six months after the incident.

A case of ingestion of "coco de mono" nuts in Venezuela containing high amounts of selenium resulted in gastrointestinal disturbances (dyspepsia, diarrhea, anorexia, and a garlic odor of the breath), neurologic symptoms (irritability, nervousness, and minor myalgias), and changes in the hair and nails.[16] The patient recovered completely. In another case, a 3-year-old boy in Australia accidentally consumed a liquid gun-bluing preparation containing 1.8% monohydrated selenium dioxide—H_2SeO_3—which led to bradycardia, slight acrocyanosis, bright red lips, hypersalivation, garlic breath, and death a few hours after ingestion.[17]

An incident occurred in 1983-1984 in the United States during which 13 persons suffered toxic effects from ingesting dietary supplement tablets containing high levels of selenium as the result of a manufacturing error.[12,13] In March 1984, selenium tablets distributed to 39 outlets in 15 states were recalled when an analysis of one lot revealed a selenium content of 27.3 mg per tablet (182 times higher than labeled). Subsequent analyses of tablets from all four implicated distribution lots showed that each tablet contained at least 25 mg of sodium selenite and 4 to 5 mg total of elemental or organic selenium.

Illustrative of the toxicity of these supplements was the case of a 57-year-old woman who had consumed 77 of the 90 tablets from a bottle when she learned of the recall and

consulted her physician. Her tablets were later found to contain 31 mg of total selenium per tablet. The woman noticed pronounced hair loss about 11 days after starting the selenium supplement in late December 1983. This progressed to almost total alopecia over a two-month period. Later, horizontal white streaking on one fingernail, along with tenderness and swelling of the fingertip and a purulent periungual discharge, was noted. These changes subsequently progressed to involve all fingernails. The fingernail from the originally affected finger was eventually lost. She also had periodic episodes of nausea and vomiting, a sour-milk breath odor, and progressive fatigue. Her alopecia was initially attributed to emotional stress consequent to the death of her husband a year earlier. She was treated with oral erythromycin for paronychia after consulting a dermatologist in January 1984. In March 1984, her serum selenium concentration was 528 ng per ml—two to four times the normal level for the US population. Her estimated cumulative dose was 2,387 mg of selenium. This woman was also taking other vitamin supplements, and selenium toxicity was thought to probably have been minimized by the simultaneous ingestion of large doses of vitamin C. Other persons who had consumed the mislabeled superpotent selenium pills had similar symptoms with varying degrees of severity.

Toxicity of Long-term Exposure

Ingesting large amounts of selenium over the long term primarily affects the pulmonary, integumentary, gastrointestinal, and central nervous systems. Symptoms observed in humans suffering from chronic selenium intoxication include depression, lassitude, nervousness, giddiness, emotional lability, dermatitis, gastrointestinal disturbances (primarily nausea and vomiting), a garlic odor of the breath and sweat, excess dental caries, and, in extreme cases, loss of hair and fingernails.[7,14] In all reported cases, symptoms and signs have abated after excess exposure ceases.

There have been no reports of disabling chronic disease or death from industrial exposures,[8] but "rose cold" is a chronic condition occurring in copper workers with exposure to elevated levels of selenium in the ambient environment. The condition is manifested by coryza, cough, and bronchitis, probably due to the production of dimethylselenide, a volatile compound excreted by the lungs and responsible for the characteristic garlic breath of selenium intoxication.

Illustrative of the chronic toxic effects resulting from occupational selenium exposure is the case of a man with a 50-year history of working in selenium refining who died of a myocardial infarction and who at autopsy had red hair and fingernails and numerous noncaseating granulomas in the lungs.[18] High selenium levels were found in the lungs, peribronchial lymph nodes, hair, and nails. The selenium level in the kidney was higher than that in the liver. In fact, there was no accumulation of selenium in the liver, as might be expected from findings in animal models. In humans the target organ of chronic selenosis appears to be the lung, which manifests acute "rose cold" or, as in this patient, a long-term granulomatous hypersensitivity. In contrast, the liver appears to be the target organ of chronic selenosis in test animals.

In areas where alkali disease in cattle has been associated with a high selenium content in soil, water, and vegetation, humans have not been similarly affected. This difference is thought to be due to the difference in human and animal diets, the wide geographic sources of food consumed

TABLE 1.—*Human Health Effects of Dietary Selenium Overexposure*

Reference Source	*Persons Involved, Location*	*Form or Source of Selenium*	*Selenium Exposure or Dose*	*Signs, Symptoms, and Outcome*
FDA, 1984[12] CDC, 1984[13]	12 cases, USA	Superpotent "health food"	Total dose 27-2,387 mg	Nausea, vomiting, nail changes, hair loss, fatigue, and irritability most common; also reported: abdominal cramps, diarrhea, paresthesias, dry hair, garlicky breath
Yang et al, 1983[14]	62-year-old man, China	Sodium selenite tablets	2 mg/tablet/d for 2 yr, equivalent to 1 mg Se/d	Thickened, fragile, honeycomb-like fingernails; gradual recovery after intake stopped
Yang et al, 1983[14]	About 50% of 248 inhabitants in 5 villages, Enshi County, Hubei Province, China	Locally grown plant crops; uptake of Se from soil originating from highly seleniferous coal	Range, 3.2-6 mg/d; average, 5 mg/d; estimated 10 yr after peak prevalence	Most common signs: nail deformation and hair and nail loss; other signs: skin lesions, tooth decay, and neurologic abnormalities Dry and brittle hair easily broke off at scalp, redicles were intact so depigmented and dull hair continued to grow; scalp rash with intolerable itching Brittle nails with white spots and longitudinal streaks on surface; effusion from around the nail New nail had rough and ridged surfaces, was fragile and thickened; broken nail advanced and fell off Skin became red, swollen, blistered, and eruptive; some followed by ulcerations that healed after a long time; primarily on limbs, also on back of neck Mottled teeth, but observation may be confounded by fluoride exposure Neurologic effects seen in one affected village included peripheral anesthesia, acroparesthesia, and dysesthesia Hyperreflexia commonly develped later, followed by numbness and paralysis; one case of hemiplegia
Science News Letter, 1962[15]	North American Indian family, Colorado	Naturally occurring underground water	9,000 μg/liter for 3 mo	Hair loss, weakened nails, listlessness
Kerdel-Vegas, 1964[16]	9 patients, Venezuela	Nuts of the "coco de mono" tree *(Lecythis ollaria)* from seleniferous areas	Brazil nuts marketed in the US have been reported to contain selenium at 100 ppm and higher	Most experienced nausea, vomiting, and diarrhea a few h after eating nuts, followed by hair loss and nail changes several wk later; foul breath in 2 patients; a 2-year-old boy died of severe dehydration; gradual hair and nail regrowth and other recovery

CDC = Centers for Disease Control, FDA = US Food and Drug Administration

by humans, and the loss of selenium during food processing.

Two field investigations in 1936 in three seleniferous areas of eastern Wyoming, southern South Dakota, and northern Nebraska suggested mild chronic selenium poisoning among persons consuming locally grown food.[19] Nonspecific symptoms of ill health such as anorexia, indigestion, generalized pallor, carious teeth, a yellowish discoloration of the skin, cutaneous eruptions, chronic arthritis, dystrophic nails, and peripheral edema were observed. A direct causal relationship was not established in either survey, however. There was also no definite correlation between the signs and symptoms seen and the selenium concentration in urine, the highest value being 1.98 μg selenium per milliliter of urine. Likewise, no control group was included in the evaluation. Most of the subjects studied were thought to have a dietary selenium intake of 700 to 7,000 μg a day, assuming an average body weight of 70 kg.

No other suggestive or documented cases of diet-related human selenium intoxication (or deficiency) in the United States have been reported, strongly suggesting that the selenium intake from the typical American diet has been both adequate and safe. The estimated requirements and other comparative dietary intake values for selenium as reported by the World Health Organization[20] are summarized in Table 2.[7,10,14,20-25]

Endemic Intoxication

An endemic chronic selenium intoxication characterized by a loss of hair and nails, skin lesions, and neurologic abnormalities occurred in China in 1961, although it was not reported until 1983.[14] The source of selenium was found to be a stony coal of unusually high selenium content (90,000 ppm), from which the element entered the soil by weathering and thereby became available for crop uptake. The daily dietary intakes of selenium, estimated ten years or more after the peak prevalence had subsided, ranged from 3.20 to 6.69 mg, with an average of 4.99 mg. Hair, blood, and urine selenium levels averaged 32.2 μg per gram, 3.2 μg per ml, and 2.68 μg per ml, respectively. The outbreak was brought on by a drought that caused a failure of the rice crop, forcing the people to consume a restricted diet consisting of locally grown vegetables and maize and few protein foods. The selenium content of corn, rice, and soybeans produced from this area was 500 to 1,000 times that of the same crops in an area of China where Keshan disease (selenium deficiency) occurred.

Heart and Motor Neuron Diseases

Although selenium has been touted in the popular press to protect against the development of coronary heart disease, the results of long-term human studies relating serum

TABLE 2.—*Human Dietary Selenium Intakes and the Associated Biologic Significance*

Country or Population	*Dietary Intake Selenium, μg/d*	*Reference Source*
Estimated requirement		
North America		
Men	80*	Levander and Morris, 1984[21]
Women	57*	
New Zealand		
Women	27*	Stewart et al, 1978[22]
China		
Men	9*	Luo et al, 1985[23]
China		
Men, endemic Keshan disease area	7.7†	Yang et al, 1985[24]
Women, endemic Keshan disease area	6.6†	
Men, nonendemic Keshan disease area	19.1†	
Women, nonendemic Keshan disease area	13.3†	
Men	40‡	
Eastern and western populations		
Adults, adequate nutrition	50-60	Combs and Combs, 1986[10]
Estimated toxic, adequate, deficient intakes		
China		
High Se area, selenosis	3,200-6,690	Yang et al, 1983[14]
High Se area, no selenosis	240	
Se adequate area	42	
Low Se area, Keshan disease	3	
Dietary intakes reported		
US		
Population intakes reported	60-216	Ganapathy and Dhanda, 1976[25]
Vegetarian diet	84	
Worldwide nutrition surveys	11-5,000, mostly 20-300	WHO, 1987[20]
Suggested adequate and safe range extrapolated from animal dietary requirement level	50-200	NAS, 1980[7]
Total body content		WHO, 1987[20]
US	14,600 μg	
New Zealand	3,000 to 6,100 μg	

NAS = National Academy of Sciences, WHO = World Health Organization

*Based on metabolic balance studies.
†Based on comparison of dietary intakes.
‡Based on plateau of plasma glutathione peroxidase activity.

selenium levels to the development of coronary heart disease are conflicting.[26]

Shamberger and co-workers concluded that the age-specific death rates for a number of heart diseases were significantly lower in regions of the US with high soil selenium levels than in regions with low selenium levels.[27] An inverse correlation between the plasma selenium level and the severity of coronary atherosclerosis also has been reported.[28] Another study showed no difference in tissue selenium concentrations between patients who died with and those who died without myocardial infarction.[29] In contrast, Salonen claimed that four Finnish studies showed supporting evidence of an increased risk of ischemic heart disease due to low selenium intake as indicated by serum selenium levels of less than 60 μg per liter[30]; three of the original studies referred to by Salonen actually reported little or no association, however.[10]

Three cases of fatal cardiomyopathy have been reported in adult male patients who received long-term (2, 6, and 7 years) total parenteral nutrition (TPN).[31-33] All three patients had low serum selenium levels. Levander discussed the importance of selenium in TPN with regard to the potential for selenium deficiency; he recommended that TPN solutions should be supplemented with selenium to provide 25 to 30 μg Se per day and that blood selenium levels should be monitored.[34]

The reported lower selenium concentrations in toenails and erythrocytes of patients with acute myocardial infarction compared with those of a matched control group were thought to be due to differences in the plant and animal components of the diet rather than the implication of selenium, or its lack thereof, in the causation of the disease.[35,36] Higher levels of selenium may serve as markers for people who eat food derived more from plants (which incorporate selenomethionine) than from animals (which incorporate selenocysteine and inorganic forms of selenium).

Selenium has also been suggested as a possible etiologic environmental factor in an unusual clustering of cases of amyotrophic lateral sclerosis occurring in four farmer-ranchers in west-central South Dakota where chronic selenium intoxication had been noted in farm animals.[10] One patient had elevated levels of selenium in blood and urine. A subsequent investigation of urinary selenium in 20 patients with amyotrophic lateral sclerosis, however, failed to show any relationship.

Teratogenicity

Experimental data on the teratogenicity of selenium have been summarized by Combs and Combs.[10] In brief, malformations were observed in chicken embryos fed a diet supplemented with 8 ppm selenium (as sodium selenite) and in chick embryos treated in ovo with selenium salts. Selenium (as sodium selenite) was not teratogenic when fed to hens at 75 ppm, given parenterally to hamsters at 2 mg per kg body weight, and administered to mice at as much as 1.8 ppm in drinking water. Seleniferous diets from pasturing on seleniferous ranges have, however, been linked to the abnormal development of embryos in pigs, sheep, and cattle.

The teratogenic potential of selenium in humans was suggested by the occurrence of several miscarriages among female laboratory technicians with exposure to selenite powder and the birth of an infant with bilateral clubfoot, but no direct causal relationship between selenium exposure and the untoward events could be established.[37]

Reproductive Effects

In natural seleniferous feedstuff, sodium selenate and sodium selenite can be embryotoxic to chickens and fetotoxic to mice, pigs, and rats.[10] Such feedstuff can reduce the growth rates of chick embryos and of fetal or neonatal mice and pigs. Rats fed seleniferous wheat diets had subnormal growth and reduced reproductive capacity. Pregnant rats given selenium in water at 1.25 and 2.5 ppm had decreased numbers of weaned pups in the second generation. At 7.5 ppm, fertility, number of surviving offspring, and growth rates of the young were reduced. Mice given selenium in drinking water from weaning through several generations had, in the third generation, fewer and smaller litters with more runts. A failure to breed and excessive deaths before weaning were also noted.

Data on semen variables and reproductive performance obtained from 125 men being evaluated for infertility have suggested a role of selenium in reproduction, although the significance of the data remains unclear.[38] A low semen selenium level was associated with a low pregnancy rate, probably resulting from male infertility because artifical insemination with donor semen resulted in pregnancies and normal births; conversely, a high semen selenium concentration was associated with elevated rates of spontaneous abortion and female reproductive failures. The data suggested that a range of semen selenium of 50 to 69 ng per ml was optimal for sperm motility and a low incidence of asthenospermia, and levels of 40 to 70 ng per ml were optimal for overall reproduction—that is, associated with a high pregnancy and low abortion rate.

Genotoxicity

Selenium has shown both antimutagenic and mutagenic properties, depending on the concentration and the chemical form used.[39] The significance of these findings is not clear. In general, sodium selenite is more mutagenic in more mutation test systems than sodium selenate.

Carcinogenicity and Anticarcinogenicity

While selenium has been alleged to be carcinogenic in laboratory animals, deficiencies in experimental design and interpretation of the lesions do not allow for a clear interpretation of the experimental data.[9,20] In particular, neoplastic lesions developed in test animals in some studies only when they had liver cirrhosis produced by overt selenium toxicity. Similarly, tumorigenic effects seen in other studies appeared to be more of a specific effect of the particular compound than of selenium itself. For example, selenium sulfide, an ingredient in certain antidandruff shampoos, has been carcinogenic for rats and female mice when given by gavage, producing hepatocellular carcinomas in male and female rats and female mice and alveolar or bronchiolar carcinomas and adenomas in female mice.[40] But selenium sulfide is a separate and distinct compound, rather than just another salt of selenium; therefore, it cannot be assumed that the results show that other inorganic selenium compounds (selenite or selenate) are carcinogenic.[9]

It also has been suggested that selenium possesses an anticarcinogenic capacity because of findings that it protected against experimental tumor induction in rats and mice, including decreased liver tumorigenesis by *N*-1-methyl-*p*-dimethylaminoazobenzene and decreased mouse skin tumors induced by 7,12-dimethylbenzanthracene.[10,41] The levels of selenium used in these studies were high, however, and nearly produced acute toxicosis in the animals.

Human epidemiologic and demographic studies do not

suggest that selenium is carcinogenic. An inverse correlation has been reported between the incidence of cancer deaths in humans and some regions of the world that are geologically rich in selenium.[42] Blood selenium levels have been reported to be lower in patients suffering from gastrointestinal cancer or liver metastases than in normal patients, although the clinical significance of such findings is unclear. A nested case-control study conducted in northwest Washington during the years 1972 to 1984 suggested that serum levels of selenium had no appreciable effect on the risk of cancer.[43] Nevertheless, the possible use of selenium as an anticarcinogenic agent has evoked experimental and preclinical research.[41,44] A more detailed discussion of the possible carcinogenic and anticarcinogenic effects of selenium is provided by the World Health Organization.[20]

Cataractogenic and Cariogenic Effects

Rats, rabbits, and guinea pigs are susceptible to selenium-induced cataracts following the subcutaneous injection of sodium selenite.[10] This is a peculiar case of selenite acting as a pro-oxidant. A period of particular susceptibility appears to exist 2 to 17 days postpartum.

Exposure to high levels of selenium during the time of tooth development also can increase the incidence of dental caries in animals. Findings from China also suggest a link between above-normal selenium intake and an increased incidence of dental caries.[14]

Interaction With Other Substances

The toxicity of selenium can be altered by interactions with other substances, including sulfate, methionine, cysteine, various heavy metals, arsenic, and vitamins C and E.[9] The function of selenium is intimately related to vitamin E in normal metabolism. It has the capacity to detoxify heavy metals by mutual interaction, but interaction between selenium and other metabolites can either reduce or potentiate selenium toxicity. Selenium can act as an antagonist against various toxic metals, such as arsenic, cadmium, copper, lead, mercury, silver, and zinc.

Nutritional Requirement and Clinical Uses

Animals

Selenium is an essential nutrient for humans and other animals, being required for normal function, growth, and reproduction. The biochemical functions of selenium that are currently recognized include its role as a component of glutathione peroxidase in animals and of several bacterial enzymes.

In animals, selenium deficiency results in stunted growth, liver necrosis, pancreatic atrophy, infertility, and white muscle disease. To be more specific, selenium has been determined to be effective in preventing or ameliorating vitamin E deficiency disorders such as exudative diathesis in chicks and turkey poults; skeletal muscle degeneration and necrosis in chickens, turkeys, ducks, lambs,

TABLE 3.—*Symptomatic Responses in Humans Associated With Selenium Supplementation*

Reference Source	*Patient Population*	*Selenium Status*	*Supplementation*	*Symptoms, Diagnoses, and Responses*
Van Rij et al, 1979[50]	31-yr-old woman	Resided in a rural area of the south island of New Zealand having low Se levels in soil and a history of endemic white muscle disease in sheep Received total parenteral nutrition fluids for intravenous (IV) feeding for 30 d after hospital admission for abdominal exploration and blood transfusion	IV infusion of 100 μg/d Se as selenomethionine	Muscle pain at rest, tenderness to palpation, pain on active and passive movement; muscle tenderness in both legs; no muscle fasciculation or neurologic deficit; returned to full mobility 1 wk after Se supplementation began
Yang et al, 1983[14]	Rural peasants with children younger than 10 yr and women of child-bearing age in Keshan County, Heilongjiang Province, northeastern China	A hypothesis regarding the etiologic role of Se deficiency was proposed because severely endemic areas coincided with areas where incidence of enzootic Se deficiency diseases in farm animals was also high	0.5 mg sodium selenite/wk if 1-5 yr old, 1.0 mg/wk if 6-9 yr old; 4,510 children in trial group, 3,985 in placebo group	Keshan disease; acute or chronic cardiac insufficiency, cardiomegaly, and arrhythmias; ECG changes are criteria for diagnosis; no symptoms or signs specific for identifying the disease Morbidity rate was 1.35% in placebo group, 0.22% in treated group; intervention trials in the following 6 yr resulted in considerably lower incidence in Se-treated children No untoward side effects observed; in some cases, nausea can be overcome by taking the supplement after meals; physical examination and liver function tests showed no adverse effects after 3-4 yr of continuous ingestion of Se
Keshan Disease Research Group, 1979[46,47]	Mostly children	Most endemic areas located in same low-Se zone as the Keshan disease; residents had low blood and hair Se levels, low urinary Se excretion, and low blood glutathione peroxidase activity	Sodium selenite at 1 mg/wk for children aged 3-10 yr and 2 mg/wk for age 11-13 yr; control groups received a placebo; total, 325 Sodium selenite, 0.5 mg/wk for children aged 1-5 yr and 1.0 mg/wk for ages 6-10 yr for 6 yr	Kaschin-Beck disease; chronic, disabling, degenerative osteoarthrosis; 1 year after treatment, x-ray film of metaphyseal changes of fingers showed a decline in the incidence of the disease; in the treated groups, 8.2% of patients showed improvement, 18.1% showed no change, but none were getting worse In the control group, 39.6% showed improvement, 41.5% showed no change, and 30% were getting worse X-ray film showed a decline in incidence from 42% to 4%

ECG = electrocardiogram

calves, and goats; hepatic degeneration in rats, mice, and pigs; testicular degeneration in rats, rabbits, hamsters, dogs, pigs, monkeys, and chickens; failure of gestation in cows and sheep; and growth retardation in immature animals of most species. The daily dietary requirements of various animal species for selenium are in the range of 0.10 to 0.20 ppm (air-dry basis).[10]

Both the amount of selenium required to prevent deficiency symptoms and the amount that will produce toxicity depend on the intake of antioxidants and protein and the presence of other feed and chemicals, the chemical form of selenium, and the age of the animal. In general, selenium in natural feedstuff is less toxic than similar exposures to selenium in water or purified feed. Dietary exposure is less toxic than parenteral or inhalation exposure. The intake of mineral and rough or high-protein feed reduces toxicity. It is important to remember that selenium's margin of safety is relatively narrow.

Humans

In patients receiving long-term parenteral alimentation, selenium deficiency may become clinically important.[31-34,45] Similarly, beneficial responses to selenium supplementation, as described later, have been observed in persons living in low-selenium areas of New Zealand and China.[45-49] The symptomatic responses seen following selenium supplementation are presented in Table 3.[14,46,47,50]

A selenium-responsive condition known as Keshan disease poses an important health hazard to peasants in China.[40,41] This is a type of cardiomyopathy most often affecting children younger than 15 years and women of childbearing age in the northern provinces and children 2 to 7 years of age in southern China. Its occurrence has been invariably associated with a low hair selenium content (generally < 0.12 μg per gram in affected areas, 0.12 to 0.2 μg per gram in unaffected areas near the affected region, and 0.25 to 0.6 μg per gram in areas removed from the affected region). Affected populations have been known to be in a selenium-poor state by urinary selenium loading tests and whole blood glutathione peroxidase activity measurements. The blood selenium concentrations of persons living in the affected areas often are less than 0.01 μg per ml, while the lowest value in unaffected areas was about 0.04 μg per liter. Clinical trials using supplemental sodium selenite showed that taking the compound was effective in reducing morbidity from the disease. Selenium administration did not cause side effects in children. Physical examination and liver function tests revealed no hepatic damage after continuous selenium administration for three to four years. Selenium deficiency accounted for most of the features of the disease, but the absence of a correlation between the seasonal prevalence of Keshan disease and the variations in hair selenium content suggest that factors other than selenium may be involved.

Selenium supplementation may also be effective in reducing the incidence and severity of Kaschin-Beck disease, an osteoarthropathy endemic to eastern Siberia, northern Korea, and parts of China.[46-48] The endemic distribution of the disease in China is similar, but not identical, to that of Keshan disease—that is, both are prevalent only in the long belt of selenium deficiency in that country.

Kaschin-Beck disease primarily affects the epiphyseal and articular cartilage and epiphyseal growth plates of growing bones. Affected cartilage shows atrophy and necrosis with repair and disturbance of endochondral ossification. The most striking feature is chondronecrosis, with proliferation of surviving chondrocytes in clusters. The condition results in enlarged joints, especially of the fingers, toes, and knees; shortened fingers, toes, and extremities; and, in severe cases, dwarfism. The characteristic enlargement of joints in patients with Kaschin-Beck disease gives rise to the name "big bone joint" disease. This disease is most prevalent among children aged 6 to 15 years but has been diagnosed as early as 13 weeks of age. It occurs more frequently in the winter and spring months. Supplemental selenium (oral sodium selenite, 0.5 to 2 mg per week) combined with vitamin E was therapeutic in 83% of patients with radiographically diagnosed disease.[46,47] Another study showed that administering sodium selenite tablets, 1 to 2 mg per week, was effective in reducing the severity and facilitating the resolution of the disease, whereas selenized table salt (20 ppm selenium) was ineffective.[49] In sum, while selenium deficiency appears to play an important role in the origin of Kaschin-Beck disease, it cannot be considered solely a selenium deficiency disorder. It is, instead, a selenium-responsive condition.

Current Trend in Dietary Supplementation

While the possible use of selenium in cancer prevention and chemotherapy has been suggested[41,43,44,51] and is the focus of clinical research, dietary selenium supplementation has also become a popular health fad, with claims being made in the popular press for the prevention of angina, arthritis, cancer, cerebrovascular disease, aging, infections, cataracts, periodontal disease, kwashiorkor, and the sudden infant death syndrome.[10,17,52] Currently, there are, however, no or insufficient data to recommend selenium supplementation as a prophylactic measure for any of these conditions, and there is reason to be concerned about overzealous selenium supplementation. Thus, at present, selenium dietary supplementation cannot be recommended on a routine basis.

Metabolism

Selenium compounds are easily absorbed from the intestinal tract.[20] In studies of rats, 95% of ^{75}Se administered by stomach tube was absorbed. Similarly, high absorption was reported in women given selenomethionine or selenite in water. The adult body burden of selenium ranges from 3 mg (New Zealand) to 14.6 mg (United States). The kidney and liver normally contain higher levels of selenium than other tissues, and muscle contains the highest proportion of the total body selenium.

Selenium is thought to be incorporated into the tissue proteins as the amino acid selenomethionine. Excretion following oral tracer doses of inorganic or organic selenium compounds in humans is mainly by the urinary tract, but naturally occurring selenium in foods is excreted equally by the urinary and intestinal tracts. High exposure also results in substantial respiratory excretion of volatile selenium compounds in animals. Whole body counting studies using single doses of ^{75}Se-labeled compounds showed an initial phase of a rapid decrease of whole body radioactivity for several days, followed by a more gradual phase of excretion. Data from studies of animals indicated that both phases of excretion were affected by the antecedent whole body burden of selenium, but the initial phase was also affected by the dose administered.

Diagnosis and Treatment of Selenium Toxicity

As previously discussed, acute selenium overexposure in humans is associated with nausea and, in some cases, vomiting and diarrhea. Acute and chronic selenosis produces nail and hair changes, peripheral neuropathy, fatigue, and irritability. A garlic odor of the breath also has been de-

scribed, although this is characteristic of several other poisons as well.

Specimens of whole blood, serum, or plasma are commonly used to measure human selenium exposure. Whole blood is thought to provide a better measure of long-term exposure. The blood selenium content, however, can be affected by the vitamin E content of the diet; exposure to inorganic mercury, cadmium, or other dietary or environmental factors; and whether the form of selenium is selenomethionine, selenate, or selenite. Urinary levels can be useful for assessing recent selenium exposure—within the past 24 hours—but must be interpreted with caution. Hair selenium content has been measured in animals, and in situations where external contamination can be positively excluded, it may be useful for assessing the selenium status in humans.

No completely satisfactory treatment of selenium toxicity is available.[53] The treatment of selenium poisoning suggested in most references has been inadequate or even misleading.[11,17] Nonspecific supportive measures that have been suggested for acute toxic ingestions include gastric lavage, respiratory assistance as needed to maintain adequate oxygenation, and the intravenous administration of fluids and vasopressors for circulatory support.[11] These general measures may be effective in cases involving a marginal lethal dosage, but they are not likely to be adequate in patients with profound overdosage.

Specific treatment with *p*-bromobenzene has been beneficial in some cases, although the hepatotoxicity of this compound effectively precludes its use in humans.[10] Another specific therapeutic intervention that has been recommended is the use of a reductant-containing bathing solution or ointment, such as 10% sodium thiosulphate, to prevent pain and necrosis in cases of burns due to a topical exposure to selenium trioxide or hydrogen selenide.[10]

Conclusion

Selenium is an essential nutrient at low levels of intake and a toxicant at high intake levels for both humans and animals. Selenium-induced toxicosis is exceedingly rare in the United States, however. Unusual cases of acute selenosis have been reported from industrial accidents, but chronic selenosis is essentially unheard of in this country because of the typical diversity of the American diet. Nonetheless, clinicians should be familiar with the possible toxicity of selenium, as well as its possible benefits, because of growing public use of this compound as a dietary supplement and because of concerns raised by the occurrence of environmental selenium contamination and resultant wildlife toxicity in several areas of the western United States.

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