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A GLOBAL VIEW OF HUMAN SELENIUM NUTRITION[1]

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This review is dedicated to Jiri Parizek, scientist, music lover, and builder of bridges between peoples.

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INTRODUCTION

During the past several years, significant advances have occurred in our understanding of the role of selenium in human nutrition and health. This is due in part to the discovery of naturally occurring human selenium deficiencies in some areas of the world. In certain other selenium-poor regions, studies on the metabolism and nutritional bioavailability of selenium have been facilitated by the low selenium status of the populations living there. As a result, research in the selenium field has rapidly acquired an international flavor.

The purpose of this review is to provide the reader with a global view of ongoing and recent work concerning the role of selenium in human nutrition and health. Previous reviews in this series have covered the biochemistry (23) and physiological effects of selenium in animals (9).

EVIDENCE FOR WORLDWIDE DIFFERENCES IN SELENIUM STATUS

Dietary Selenium Intakes

Selenium is efficiently transferred up the soil-plant-animal-human food chain so that geographical differences in the availability of the selenium in soil for uptake by plants account for most variations in the selenium content of foods (54). Estimates of adult daily dietary selenium intakes worldwide range over more than three orders of magnitude. The most extreme values have been reported from the areas of human selenium deficiency (Keshan disease) and toxicity in the People's Republic of China, 7 and 38,000 μg/day, respectively (140). Less extreme values for low dietary selenium intakes, 28–30 μg/day, have been observed in New Zealand and Finland (120, 125). Intakes in Caracas, Venezuela are somewhat elevated (218 μg/day) because an important agricultural production area in that country is located in a seleniferous zone (79). In the United States (US), intakes often tend to fall within the estimated safe and adequate range of 50–200 μg/day (96, 133) established by the US National Research Council in 1980 (86). However, there are certain exceptions [e.g. some higher values are reported from South Dakota (93)].

Many of the problems associated with obtaining accurate estimates of dietary selenium intakes have been discussed previously (60). For example, calculated values based on food composition and consumption data can be misleading if the composition data for selenium have not been derived from foods representative of those consumed by the population being studied. If, on the other hand, the selenium data base is generated from foods consumed in a restricted geographical area, there is a good correlation between calculated intakes and intakes determined by actual chemical analysis (133). In

some countries with low-selenium soils, there can be significant annual changes in the dietary selenium intake because of importation of high-selenium grain from other countries (81, 130).

Attempts to assess selenium status by determining dietary selenium intake are complicated by the fact that the nutritional bioavailability of the selenium in different foods is not the same (56). An animal model based on the restoration of hepatic glutathione peroxidase activity in selenium-depleted rats has shown that the bioavailability of selenium in mushrooms and certain seafoods is less than that in wheat or Brazil nuts (13, 26, 82). Studies carried out with persons of low selenium status in Finland, New Zealand, and China indicate that selenium fed as selenomethionine, high-selenium wheat, or selenium-rich yeast is retained better in the body than selenium given as selenate or selenite, even though all these forms of selenium were more or less equivalent in elevating glutathione peroxidase activity in various blood fractions (62, 71, 121). The complex metabolism of various selenium compounds precludes equating bioavailability with simple absorption measurements and suggests the need to develop more sophisticated criteria for determining the nutritional availability of selenium in foods.

Blood and Tissue Selenium Levels

On a global scale, the content of selenium in the blood tends to be lowest in those areas of the world with low dietary selenium intakes (Keshan disease areas of China, New Zealand, Scandinavia) and highest in areas with high dietary intakes (Villa Bruzual, a seleniferous zone in Venezuela, and areas of human selenosis in China) (55). Blood selenium level is generally considered a good index of selenium status in persons who are in equilibrium with their environmental and dietary exposure to selenium, although there are certain situations in which blood levels give misleading results (58). Plasma selenium content reflects shorter-term selenium status than whole-blood selenium.

Much less is known about the selenium content of various human tissues and organs, but again the limited data indicate that the amounts found in the human body tend to reflect the reported dietary intake. For example, the total-body selenium content of North Americans as estimated from autopsy data ranged from 13 to 20 mg (108), whereas the total-body content of New Zealanders as determined by radiotracer turnover studies was only 3 to 6 mg (114). Likewise, the individual tissues of New Zealanders contained less selenium than those of North Americans (12). In particular, the selenium content of the skeletal muscle of New Zealanders was only one sixth to one fourth as great as that of North Americans. This is an important difference since, at least in North Americans, the selenium pool in skeletal muscle can account for almost half the total-body selenium content (58) and thereby serve as a significant storage reservoir for selenium in times of need.

Glutathione Peroxidase Activity

At the present time it is not possible to compare glutathione peroxidase activity data from various laboratories because no standardized method for measuring the enzyme activity has been widely accepted and slight changes in technique can cause large differences in the results obtained. However, data generated within a given laboratory that has the method under control can be compared. In New Zealand subjects of low selenium status, a linear correlation was observed between blood glutathione peroxidase activities and whole-blood selenium levels up to 0.1 μg/ml or red cell selenium levels up to 0.14 μg/ml (97, 119). Above these concentrations, the enzyme activity tended to plateau and no relationship was seen with blood or red cell selenium content. This is an important limitation on the use of glutathione peroxidase activity to assess selenium status since in those countries with moderate or high dietary selenium intakes most individuals will have blood selenium levels above this cutoff point. Even in an area of the US with relatively low-selenium soils, for example, only one subject of 147 tested had red cell selenium levels consistently less than 0.14 μg/ml (112). Several groups have now shown that it is possible to elevate glutathione peroxidase activity in various blood fractions from individuals of low selenium status by supplementing them with certain selenium compounds (62, 71, 121).

EFFECTS OF LOW SELENIUM INTAKE ON HUMAN HEALTH

Keshan Disease

Keshan disease is an endemic cardiomyopathy that has been recognized in China for more than a century (33). Its name comes from an episode in 1935 in which 57 of 286 inhabitants of a village in Keshan county of Heilongjiang Province in northeast China died of the disease in two months (69). Since the cause of the disease was unknown, it was named after the location of this serious outbreak. The disease is geographically restricted to mountainous and rural areas scattered along a belt that extends from northeast to southwest China (137). The populations at risk consist mainly of young peasant women and children living in rural areas. The limited and unvaried diet of these peasants probably accounts for their susceptibility to the disease (116, 142). The incidence of the disease varies seasonally, with peaks occurring in the south during the summer and in the north during the winter.

Keshan disease presents a broad spectrum of clinical features related to cardiac involvement and can be divided into four types: acute, subacute, chronic, and latent. No specific test exists for the disease and its diagnosis must be a clinical judgement based on established criteria (16, 69). Myocar-

dial diseases of unknown cause are not rare in China, but Keshan disease can be clearly differentiated from myocarditis or other types of primary or secondary cardiomyopathy by its characteristic histopathology (69). Multifocal necrosis and fibrous replacement of the myocardium are the main pathological features of the disease (33, 38, 67); the focal nature of the pathology distinguishes Keshan disease from viral myocarditis with which it was at first confused (25). Electron microscopy showed swollen mitochondria (33, 67) with triple membrane structures occurring at the widened interspace of the cristal membranes (33). Electron-dense granules morphologically distinct from virus particles were also observed (33, 69).

The etiology of the disease was clarified when it was realized that white muscle disease, a selenium–vitamin E deficiency of lambs and calves that affects both heart and skeletal muscle, occurred in certain endemic areas of Keshan disease (69). Research workers at Xian Medical College suggested that Keshan disease is also probably a form of endemic cardiomyopathy that results from selenium deficiency (69). The Keshan Disease Research Group of the Chinese Academy of Medical Sciences (now the Chinese Academy of Preventive Medicine) carried out extensive nationwide epidemiological studies of the etiologic relationship of selenium to Keshan disease (69). It was discovered that the dietary intakes and blood levels of selenium of persons living in the endemic Keshan disease areas were the lowest ever recorded anywhere in the world.

Because of these epidemiological relationships, selenium supplementation has been used on a large scale in China as a preventive measure against Keshan disease. Some indication of the success of these programs can be obtained by considering a study in Sichuan Province during 1976–1980 (137) in which the incidence rate of Keshan disease was 1,713 among 1,107,568 untreated subjects (1.55 per 1000) versus 88 among 323,872 subjects treated with selenium (0.27 per 1000). The dosage used in these studies was 0.5 and 1.0 mg of sodium selenite weekly for children 1–5 and 6–9 years old, respectively. Many other studies carried out in several provinces of China on millions of people have all shown that sodium selenite given orally was effective in reducing the incidence, morbidity, and fatality of Keshan disease (137).

Low selenium status appears to play the primary etiologic role in Keshan disease, but some features of the disease cannot be explained solely on the basis of selenium deficiency (140). For example, the seasonal variation in the disease is not accompanied by changes in body selenium stores, as assessed by levels of selenium in the hair. Some geographical inconsistencies have been noted also: not all selenium-deficient areas are necessarily endemic. Moreover, no differences were seen in blood selenium levels between healthy and diseased children from the same affected area. Vitamin E nutrition does

not seem to be a complicating factor since there was no significant difference in plasma vitamin E concentration between affected and unaffected individuals, although both groups could be considered to have borderline adequate levels (140). Insufficient dietary methionine may contribute indirectly to Keshan disease by decreasing the nutritional bioavailability of selenium, but this hypothesis needs further testing (140).

The search for secondary factors in Keshan disease led to the suggestion that various toxins, hypoxia, or infectious agents, particularly viruses, were involved (137). The viral hypothesis is especially appealing since selenium-deficient mice showed an increased susceptibility to the cardiotoxic effects of a Coxsackie B_4 virus that had been isolated from an individual with subacute Keshan disease (4). Although it seems clear that Keshan disease results from a combination of factors, the preventive effect of selenium indicates that selenium deficiency is the fundamental condition predisposing a person to the disease.

For almost half a century following the severe outbreak in 1935, Keshan disease was a serious public health problem in many areas of China. However, in recent years improvements in medical care and living conditions have brought about a significant decline in the disease (69). The study of Keshan disease patients may become more difficult in the future because of the diminishing number of new cases. Thus, an animal model of the disease would be very useful, but so far no experimental animal has been found to be ideal for that purpose (137). Nonetheless, changes in the myocardial parenchyma and increases in heart weight have been observed in white rats fed corn and vegetables grown in the endemic areas (see references 12 and 13 cited in reference 116). Likewise, swine fed grain from endemic areas for six months exhibited multiple myocardial necrosis as well as other lesions (see references 39 and 40 cited in reference 38). Also, vitamin E deficiency exacerbated the pathological and histochemical changes in the heart and liver of piglets fed a low-selenium diet composed mainly of cereals grown in the Keshan disease area (137). An attempt to potentiate adriamycin-induced cardiomyopathy in rats by feeding a selenium-deficient diet was unsuccessful even though the deficiency exacerbated other toxic effects of the drug (15).

Kashin-Beck Disease

Kashin-Beck disease (Osteoarthritis deformans endemica) is an endemic osteoarthropathy that occurs in northern China, North Korea, and eastern Siberia (88). Its name comes from the Russian investigators who first described and provided detailed clinical accounts of the disease (88). An estimated two million persons are affected in the People's Republic of China (126) and the disease has been declared a national priority health problem (113).

This disabling polyarticular degenerative joint disease typically has its onset during the first or second decade of life (113). Preadolescent and adolescent children initially present with symmetrical stiffness, swelling, and often pain in the interphalangeal joints of the fingers. At this stage, it is said that the disease can be reversed. Then the disease progresses to a generalized osteoarthritis involving elbows, knees, and ankles, with possible locking of the joints by the third decade (113). Failure of bone development due to epiphyseal impairment leads to shortened fingers and toes and, in extreme cases, dwarfism (78). Secondary osteoarthrosis with joint disfiguration can arise from chronic pathological changes in the articular cartilage. Hence, the disease is also called Dagujie disease ("enlarged joint" disease) in China. In addition to the cartilage and bone changes, atrophy is commonly found in the striated muscular tissue of the extremities. The most important pathological feature of the disease is a multiple focal chondronecrosis (78).

At present there are three major hypotheses concerning the etiology of Kashin-Beck disease: a generalized imbalance of macro and trace elements (101); poisoning by *Fusarium* mycotoxins (88); and nutritional deficiency of selenium (70, 78). The selenium deficiency hypothesis was suggested by animal experiments in which rats fed cereals from an endemic area died of acute massive liver necrosis (78). Fluorimetric analysis confirmed the low selenium content of the feed from the disease-affected area. Studies on the relationship between the urinary selenium level and the incidence of the disease in children as detected by x-ray examination resulted in clear-cut dose-response curves (78).

An uncontrolled therapeutic trial showed that more than 80% of the children treated with sodium selenite and vitamin E exhibited some improvement in their condition, but the response was limited only to patients who were in the early stages of Kashin-Beck disease (70). The selenium was given orally as a 0.15% solution of sodium selenite once a week for 3 to 6 months. The dose was 0.5, 1.0, or 2.0 ml for children $\leq$ 5, 6–10, or $\geq$ 11 years old, respectively. The vitamin E was given intramuscularly at a dose of 100 mg/week or orally at 15 mg/day. A similar result was obtained in a controlled therapeutic study: 82% of the children in the selenium-treated group improved after a year (68). The weekly dose here was given in the form of tablets containing 1 or 2 mg of sodium selenite for 3–10 or 11–13 year olds, respectively. However, almost 40% of the children in the control group (starch placebo tablets) also showed some improvement even without selenium treatment. On the other hand, the condition of about 19% of the children in the control group got worse over the course of the study, whereas none of the selenium-supplemented children showed any signs of deterioration.

An intervention trial carried out with selenized salt over a five-year period to test the prophylactic efficacy of sodium selenite against Kashin-Beck

disease failed to demonstrate any difference between the control and treated groups (68). However, this study was conducted against a background of steadily improving economic and social conditions in rural China, and the better diet available to the peasants may have masked any preventive effect of the selenium.

Certain observations appear inconsistent with the hypothesis that selenium deficiency is a causal factor in Kashin-Beck disease. Rats fed low-selenium cereals from the endemic area developed atrophy of the epiphyseal growth plate but the chondronecrosis of the cartilage tissue typical of Kashin-Beck was not observed (78). Likewise, low-selenium semisynthetic diets in rats induced atrophy of the epiphyseal growth plate but no cartilage necrosis. Furthermore, rabbit or human infant chondrocytes grown in vitro exhibited no idiosyncratic requirement for selenium (132).

Both Keshan disease and Kashin-Beck disease are found in the low-selenium regions of China, but the geographical distribution of these diseases is not altogether coincident (117). This indicates that etiological factors other than selenium deficiency are involved. In the case of Keshan disease, a cardiotoxic virus was indicated as a possible agent (see above). A slow virus has been suggested as a possible causative factor in Mseleni joint disease, an endemic crippling generalized osteoarthritis found in northern Zululand (89), but any role for a virus in Kashin-Beck disease is unknown.

The tibial dyschondroplasia induced in chickens by feeding a toxin isolated from cultures of *Fusarium roseum* was suggested as a possible animal model of Kashin-Beck disease (53). Epidemiologic evidence supports roles for selenium deficiency as well as *Fusarium* mycotoxicosis in the etiology of Kashin-Beck disease (113), and selenium status is known to have diverse effects on the metabolism and toxicity of various xenobiotic compounds (9, 23). However, selenium deficiency had no influence on the development of *Fusarium*-induced tibial dyschondroplasia in broiler chickens (127).

Total Parenteral Nutrition

Solutions used for intravenous feeding (total parenteral nutrition; TPN) are practically devoid of selenium (57). As a result, patients administered TPN without selenium supplementation run the risk of developing selenium deficiency. Several instances of biochemical selenium deficiency (decreased blood selenium levels and/or glutathione peroxidase activities) due to TPN have already appeared in the literature. Not surprisingly, the first description of a clinical selenium deficiency in TPN involved a patient from New Zealand, a country with low-selenium soils (124). This patient developed muscle pain and tenderness in the thighs that responded within a week to supplementation with 100 μg of selenium per day as selenomethionine. No consistent characteristic clinical syndrome caused by selenium deficiency has

yet been observed in TPN patients (63). However, case reports have linked muscle pain or weakness (8, 48, 124) or cardiomyopathy (31, 47) to selenium deficiency.

Selenium supplementation seems appropriate for certain classes of TPN patients but what is less clear is the correct dosage and chemical form of selenium to be administered (57). At the present time, the American Medical Association has no official guidelines for the parenteral use of selenium. A workshop of the American Society of Parenteral and Enteral Nutrition convened to address this issue did not develop a consensus because of differing views concerning what constituted an adequate supply of selenium (63). As more and more instances of TPN-induced selenium deficiency are discovered, the need for such guidelines becomes more apparent.

Associations of Selenium with Cancer

Early animal studies suggested that certain forms of selenium might be carcinogenic. Feeding a low-protein diet containing high levels of selenium as seleniferous grain or as mixed inorganic selenides to rats resulted in liver cell adenomas or low-grade carcinomas that accompanied hepatic cirrhosis (87). Subsequent work by others failed to demonstrate any neoplasms attributable to selenium in rats fed sodium selenite or selenate under a variety of conditions (39). Administration of high doses of selenium sulfide, a component of some antidandruff shampoos, by gavage caused an increased incidence of hepatocellular carcinoma in male and female rats and of hepatocellular and alveolar-bronchiolar carcinomas in female mice (83). However, dermal application of either selenium sulfide or Selsun,® an antidandruff shampoo, did not produce a carcinogenic effect in mice (84, 85).

Possible anticarcinogenic properties of selenium were reported in animal studies as early as 1949 (20), but the real impetus to further research in this area came from a number of geographical observational studies suggesting that cancer mortality rates were inversely related to the geographic distribution of selenium (107, 110, 141). Although the pitfalls of such ecological comparisons are well known (22, 103), these cross-population studies played an important role in generating hypotheses and stimulating additional research. Several case-control studies have now appeared in which cancer patients were shown to have lower blood selenium levels than controls, but interpretation of these results, with the possible exception of one study dealing with skin cancer (22), is complicated by the fact that the disease process itself may have influenced the selenium status of the patients involved.

Two individual-based prospective studies from Finland support an inverse relationship between selenium status and the risk of cancer (103). In the first study, in which samples were collected in 1972, serum selenium levels for

cases and matched controls were 51 and 54 μg/liter, respectively, whereas in the second study (samples collected in 1977), the levels in cases and controls were 54 and 61 μg/liter, respectively. The upward drift in serum selenium levels for both cases and controls between 1972 and 1977 was attributed to an increased importation of high-selenium grain into Finland during the late 1970s (81). A prospective study from the US also in agreement with an inverse relationship between selenium status and cancer risk showed that the prediagnostic serum selenium level of 111 cancer patients was 129 μg/liter while that of 210 cancer-free matched controls was 136 μg/liter (135). Three subsequent prospective studies from the US failed to demonstrate any dose-response relationship between baseline serum selenium levels and risk of subsequent cancer (21, 94, 105), and another was suggestive of a direct relationship between serum selenium levels and risk of lung cancer (75).

Occupational experience with workers in a selenium rectifier plant in western England revealed no effect of selenium, favorable or unfavorable, on the death rate due to malignant neoplasms (35). Recent information from Sweden indicates that lung cancer in smelter workers was associated with low levels of selenium and high levels of cadmium in lung tissue (34). Since selenium is known to inhibit the growth stimulatory effect of cadmium on human prostatic epithelium (131), the elevated cadmium/selenium ratios in the lungs of these workers could explain their increased susceptibility to lung cancer. Chinese tin miners were shown to have lower blood selenium levels and higher age-adjusted lung cancer mortality rates than residents of Beijing (17).

The epidemiological findings (along with certain animal experiments, see below) have created much interest in the possible use of selenium compounds as potential cancer chemoprevention agents (14, 19, 24, 136). However, the age-adjusted mortality rates for breast and colonic cancer reported in the United States are considerably higher than those reported in Finland (129) even though the dietary selenium intakes are much higher in the US. The low risk of large bowel cancer in Finland is thought to be due to the high consumption of dietary fiber there (98). Thus, it appears that any possible effect of dietary selenium in the etiology of human cancer could be masked or overcome by the influence of other food constituents.

A voluminous literature based on many animal studies shows that under certain conditions relatively high dietary levels of selenium can have a protective action against a variety of chemically induced, spontaneous (possibly virally induced), and transplantable tumors in rats and mice (comprehensively reviewed in 42 and 77). Moreover, high levels of selenium given in the drinking water protected against UV-light-induced skin cancer in hairless mice (92). By comparision, few studies have examined the effect of selenium deficiency on experimental cancer. Ip & Sinha (44) found that

selenium deficiency increased the tumorigenic potency of dimethylbenz-[a]anthracene (DMBA) to the rat mammary gland when diets high in polyunsaturated fat (25% corn oil) were fed. The potentiation of DMBA tumorigenicity by selenium deficiency was not seen in rats fed low-fat diets containing polyunsaturated fat (1–5% corn oil) or in rats fed diets high in saturated fat (24% coconut oil plus 1% corn oil). This effect of selenium deficiency in increasing the susceptibility of rats to the carcinogenic action of DMBA may be related to selenium's antioxidant function at nutritional levels as a constituent of the active site of glutathione peroxidase. On the other hand, Pence & Buddingh (95) showed that dietary selenium deficiency had no effect on the incidence and size of 1,2-dimethylhydrazine-induced colon tumors in rats. Moreover, Reddy & Tanaka (99) found that selenium deficiency significantly *inhibited* the incidence and multiplicity of colon tumors induced by azoxymethane in male rats. The biochemical mechanism by which selenium deficiency could protect against cancer is not clear, but it is known that the activity of certain subunits of hepatic glutathione-S-transferase is increased in rats made deficient in selenium (74).

A number of reports suggest that even high dietary levels of selenium do not always protect against experimental cancer in animals. Most workers agree that the upper limit of dietary selenium in animal nutrition experiments is about 0.25 μg/g (19). For example, Thompson & Becci (118) observed that 5 μg/g of dietary selenium had no effect on the incidence of tracheal tumors induced in hamsters by 1-methyl-1-nitrosourea. These authors attributed their negative result to the fact that a direct-acting carcinogen was used (i.e. a carcinogen active in itself and not requiring metabolic activation). However, Beems (5) showed that similar dietary levels of selenium had no influence on the tumor response in the respiratory tract or other organs of hamsters after the intratracheal instillation of the indirect-acting carcinogen benzo[a]pyrene. Elevated dietary intakes of selenium also had no effect on the incidence or number of forestomach tumors induced in mice by benzo[a]pyrene (6). Aquino et al (3) found that 2 μg of Se per gram of diet had no inhibitory effects in a two-stage rat model of hepatocarcinogenesis induced with diethylnitrosamine and promoted with phenobarbital.

LeBoeuf et al (51) investigated the effects of dietary selenium on the development of enzyme-altered liver foci and hepatocellular carcinoma induced by diethylnitrosamine or N-acetylaminofluorene and promoted by phenobarbital in rats. They concluded that selenium can increase or decrease the carcinogenic process depending on the dietary selenium level, the duration of selenium feeding, and the experimental system studied. Ankerst & Sjögren (2) reported that administration of 4 μg of Se as sodium selenite per milliliter of drinking water stimulated and inhibited the induction of small- and large-bowel cancer, respectively, in the same rats treated with 1,2-dimethylhy-

drazine. These authors also noted that similar selenium treatment greatly facilitated the induction of breast fibroadenoma by adenovirus type 9 in the rat.

Selenium had no effect on the induction of neoplasia by Rauscher leukemia virus in mice (30). The type of diet fed had a marked influence on the ability of selenium to protect against spontaneous mammary tumors in mice (134). Birt (7) found that selenium increased pancreatic carcinoma yields in male hamsters fed a high-fat diet and treated with N-nitrosobis(2-oxopropyl)amine and urged that caution be used in administering selenium compounds to humans for cancer prevention.

Several hypothetical mechanisms have been proposed to account for the possible protective effects of high dietary levels of selenium in animal tumor model systems, including alleviation of carcinogen-induced oxidative damage, alterations in carcinogen metabolism, and selective toxicity to rapidly dividing cells (22). At high dietary levels any protective effect of selenium apparently is unrelated to its antioxidant role in glutathione peroxidase (43, 73). Protective effects of dietary selenium have been observed during both initiation and promotion phases of carcinogenesis, so there is little evidence to suggest that selenium interferes with carcinogen metabolism and/or binding to DNA (43). LeBoeuf et al (52) postulated that the antiproliferative effect of selenium on cells may result from elevations in the intracellular GSSG/GSH ratio. Selenium status may modulate the thromboxane/prostacyclin ratio in vivo (see next section) and thereby influence tumor cell–platelet interactions involved in the ability of neoplasms to metastasize (76). More research is obviously required to clarify under which conditions selenium may have an anticarcinogenic effect and the biochemical mechanism(s) responsible for such an effect.

Associations of Selenium with Heart Disease

Epidemiological evidence in support of the possible role of low selenium status in the pathogenesis of cardiovascular disease derives from ecological observations, case-control comparisons, and prospective studies. Cross-sectional and case-control studies suffer from inherent biases, however, and have contributed little to our understanding about selenium and atherosclerotic cardiovascular disease (104).

Five prospective epidemiological studies have been published to date, all from Scandinavia. One study found an inverse association between selenium and the risk of death from ischemic heart disease, two were equivocal, and two found no association (104). On the basis of these five studies, no causal relationship could be established between selenium status and the risk of ischemic heart disease. However, it was concluded that these Scandinavian studies did not dismiss the hypothesis of an inverse association between serum

selenium concentration and the risk of ischemic heart disease under conditions of low selenium intake, as indicated by mean blood and serum selenium levels of 60 and less than 45 μg/liter, respectively (104). Studies from England (28) and New Zealand (100) failed to detect any correlation between the traditional risk factors for cardiovascular disease and blood selenium levels or glutathione peroxidase activities.

Animal experiments have suggested a plausible biochemical mechanism by which low selenium status could play a role in the development of cardiovascular disease via effects on arachidonic acid metabolism. Selenium deficiency increases the production of the proaggregatory metabolite thromboxane B_2 by rat platelets, whereas biosynthesis of the antiaggregatory metabolite prostacyclin by rat aorta is impaired (106). The enzyme responsible for prostacyclin formation, prostacyclin synthase, is inhibited by elevated levels of lipid hydroperoxides (128), which could arise because of depressed glutathione peroxidase activity during selenium deficiency. The relative importance of glutathione peroxidase and other peroxidases in destroying lipid hydroperoxides, however, still needs to be clarified (111).

Is Selenium Involved in Kwashiorkor?

Klaus Schwarz, discoverer of the nutritional essentiality of selenium, attempted to link selenium deficiency with kwashiorkor in some of his clinical studies (109). This was a logical connection since selenium tends to be associated with protein in foods (54), and diets low in protein might be expected to be low in selenium as well. Moreover, Schwarz believed that the commonly accepted interpretation of kwashiorkor solely as a disease of protein malnutrition did not adequately explain all clinical aspects of the disease (109).

For these reasons, he carried out a preliminary study in Jamaica with two children suffering from kwashiorkor who had very slow weight gains after having overcome the initial, acute phase. These children, who had not gained weight for 2 and 5 weeks, respectively, responded immediately with weight gains after treatment with selenium (109). This weight gain was also accompanied by an increase in food intake. Hopkins & Majaj (41) were able to demonstrate growth and reticulocyte responses in three marasmic infants from Jordan after treatment with 30 μg of selenium per day as sodium selenite. Fondu et al (32) suggested that selenium deficiency could play an important role in the pathogenesis of the anemia of protein-energy malnutrition observed in the Kivu province of the Republic of Zaire.

Burk et al (10) showed that blood selenium levels in Guatemalan children with kwashiorkor were less than half those of control children. However, much of the difference between the two groups was due to differences in plasma selenium levels; when the plasma selenium content was expressed on

a protein basis, no significant difference was found between the groups because of the marked hypoproteinemia in the kwashiorkor cases. It is now appreciated that alterations in plasma selenium levels may be secondary to changes in plasma protein concentrations (1). On the other hand, plasma selenium levels were reduced in Thai children suffering from protein-calorie malnutrition, even when expressed on a plasma protein basis (66).

Burk et al (11) were careful to point out that their results were not intended to imply that children with kwashiorkor were selenium deficient. They did believe, however, that their results demonstrated reduced selenium stores in such children. At any rate, the concept that selenium deficiency played an etiological role in kwashiorkor was not widely accepted. More recently, Golden et al (36) presented their provocative hypothesis that kwashiorkor could be precipitated by a number of oxidant stressors (e.g. iron overload). Such stresses could initiate free radical chain reactions in children with inadequate antioxidant defense mechanisms, particularly glutathione peroxidase. In fact, Golden & Ramdath (37) said that they could predict which children would subsequently die of kwashiorkor and which would survive on the basis of their admission red cell glutathione peroxidase activity and plasma ferritin concentration (indicative of iron overload). More research is obviously indicated to test this controversial theory concerning selenium and kwashiorkor.

Oxidative Stress and the Malarial Parasite

Oxidative stress is experienced by red blood cells during malarial infection, as evidenced by an increased production of malonyldialdehyde (115). The malarial parasite itself apparently generates oxidants within infected erythrocytes to render the infected cell less able to prevent or repair oxidant damage (29). This increased susceptibility of parasitized red cells to oxidant damage led to the suggestion that free oxygen radical generators might be useful antimalarial drugs. For example, intravenous injections of *t*-butyl hydroperoxide successfully reduced parasitemias in mice infected with *Plasmodium vinckei* (18). The destabilizing effect on the infected erythrocyte of the combined oxidant stresses due to the parasite and the exogenously supplied free radical generator is thought to cause premature lysis of the red cell. The attendant early release of immature noninfectious parasites leads to a limited, rather than fulminant, infection. Another peroxide-containing compound that exhibits antimalarial activity is qinghaosu, a constituent of an herb long known in Chinese traditional medicine (49). Although the exact mechanism of action of qinghaosu is not known, its antimalarial activity may be due to free oxygen radicals released in degradation of the peroxide linkage of the compound (18).

Deficiencies of certain nutrients with antioxidant properties such as selenium, vitamin E, vitamin C, and riboflavin (via its role in regulating in-

tracellular glutathione levels) depress the development of malarial parasites in experimental hosts (27, 80, 122, 123). Under these conditions, the infection apparently is limited by the premature lysis of the red cell brought about by the combined oxidant stresses of the parasite and the deficiency of the antioxidant nutrient. Refeeding malnourished human populations in Africa has been associated with the recrudescence of latent malarial infections (123). It was suggested that vitamin E deficiency might limit the severity of malarial infection in malnourished herding peoples of Eastern Niger (27), whereas low selenium status may have afforded some protection against the parasite in Somali nomads (80).

Recently, attempts have been made to potentiate the therapeutic activity of qinghaosu against experimental rodent malaria by feeding mice diets deficient in certain antioxidant nutrients. Low selenium status did not appear to improve the antimalarial potency of qinghaosu in mice infected with *P. yoelii* (61), but vitamin E deficiency markedly enhanced the therapeutic effect of the drug as judged by either increased survival or decreased parasitemia (A. L. Ager, R. May, and O. A. Levander, unpublished observations). Whether manipulation of the antioxidant status of the host will ever have any useful therapeutic application against human malaria is a question that can only be answered by future research.

EFFECTS OF HIGH SELENIUM INTAKE ON HUMAN HEALTH

A detailed account of the toxic properties of selenium compounds is beyond the scope of this review, and the reader is referred to the recent paper by Olson (91). He suggested a maximum safe multiple oral intake over extended periods of 5 μg of selenium per day per kg body weight for adults (i.e. 350 μg per day for a 70-kg man). Other estimates of maximum allowable intakes include 500 μg per day, based on Japanese populations that eat large amounts of fish (102), and 750 μg per day, based on dietary intakes in a high-selenium area of China where chronic human selenium toxicity was not observed (138).

At present, no sensitive biochemical indicator of selenium overexposure is known. A garlicky breath odor has been used to monitor selenium exposure in industrial workers (35). One of the most consistent signs of human selenosis in areas of naturally high dietary selenium intake is a change in the fingernails. Such changes have been observed in some persons residing in high-selenium areas of the US (91), Venezuela (45), and China (138). Nail changes and hair loss were observed in several individuals in the US who had ingested a superpotent over-the-counter "health food" supplement containing selenium (40, 46). Because of a manufacturing error, this product contained 182 times more selenium than was stated on the label. Peripheral neuropathy was also

seen in some of these cases, in agreement with the nervous system abnormalities reported in China (138). This episode of human selenium poisoning due to supplement use demonstrates the toxic potential of these preparations.

Recent findings from California, US, suggest that under some conditions selenium may play a role as an environmental contaminant (90). Irrigation waters draining certain soils of high selenium content apparently contained enough selenium to cause reproductive problems in the aquatic birds nesting on ponds of such drainwater. Breast muscle from one species of bird (American coot, *Fulica americana*) had an average selenium content of over 3 μg/g fresh tissue. This prompted the California State Department of Health Services to issue a health advisory recommending that "adults not consume more than one meal per week of coots from this area, and that *no* coots from this area be eaten by children or pregnant women" (90). Additional research is needed to determine the significance of this problem in the western United States.

DIETARY STANDARDS FOR SELENIUM

Methods for Estimating Human Selenium Requirements

Since 1980, there has been considerable progress in determining human nutritional requirements for selenium. Prior to that time, the only way to estimate human selenium requirements was to extrapolate from the results of animal experiments. However, the selenium requirement of animals can vary by an order of magnitude depending on the species chosen and the criterion of deficiency selected (59). Thus, that approach is not very helpful in precisely delineating selenium requirements for humans.

During the past several years, a number of human studies have appeared in which various methods were used to estimate the selenium requirements of people. Among the techniques employed were metabolic balance studies, comparison of dietary intakes in areas with and without Keshan disease, and measurement of glutathione peroxidase activity in subjects of low selenium status before and after selenium supplementation. Although metabolic balance studies have had a long history in determining mineral requirements, the limitations of this approach became obvious when such studies were carried out to estimate human selenium requirements. Healthy North American men needed about 80 μg of dietary selenium per day to maintain balance, whereas Chinese men living in a low-selenium area needed only 9 μg per day (64, 72). This great discrepancy in the amount of selenium needed for metabolic balance in these two adult populations can be explained largely on the basis of differences in total selenium body pool sizes in these two groups of men. The

total body pool sizes are in turn largely a function of habitual dietary selenium intake (although body size may also have an influence here; see, for example, the differences in the amounts of selenium needed to maintain balance in North American men vs women in Ref. 64). Thus, selenium balance at intakes above minimum requirements is determined largely by equilibrium input and output and does not give a true indication of human requirements.

Dietary selenium intakes in areas of China with and without human deficiency (i.e. Keshan disease) were used to estimate minimum human requirements for selenium. Only 7.7 and 6.6 μg of selenium per day were consumed in endemic areas, and 19.4 and 14.1 μg/day in nonendemic areas, for male and female adults, respectively (139). The intakes reported in the nonendemic areas probably approximate minimum requirements for selenium.

An attempt to estimate the selenium requirement of young North American men using a depletion-repletion regimen did not succeed because the body selenium reserves of the subjects kept their plasma selenium levels high relative to the levels commonly reported in Finland or New Zealand, even after 7 weeks of depletion (65). Chinese men of very low selenium status (dietary intake of 10 μg/day) were repleted with various levels of selenomethionine, and all men supplemented with 30 μg of selenium or more daily eventually achieved similar plasma glutathione peroxidase activities (139). On this basis, a selenium requirement to saturate glutathione peroxidase activity of about 40 μg/day (diet plus supplement) was suggested for Chinese adult males. To be applicable to other population groups, this figure presumably would have to be adjusted for differences in body size.

The above examples demonstrate the recent rapid advances that have occurred in our understanding of the dietary intakes of selenium needed to prevent nutritional deficiency diseases in humans. Whether or not pharmacological intakes of selenium have any additional beneficial effects against human degenerative diseases such as cancer or heart disease remains a problem for future research.

Current and Projected Dietary Selenium Standards

The only current dietary standard for selenium is the estimated safe and adequate daily dietary intake of 50 to 200 μg per day for adults, suggested by the US National Research Council in 1980 (86). Scientists often mistakenly refer to the RDA for selenium when there actually is no Recommended Dietary Allowance for this essential trace element. Rather, the scientific data on which the safe and adequate dietary selenium intake was based were less complete than those for nutrients with established RDAs.

That was certainly the situation in 1980 but, as discussed above, our understanding of human selenium requirements has increased greatly since then. It is now possible to define a reasonable dietary recommendation for

selenium based on the elegant repletion studies conducted by Yang and associates in the People's Republic of China (139). The physiological requirement derived by those scientists was 40 μg per day for Chinese men weighing about 60 kg (G. Yang, personal communication). Since the requirement for selenium appears to be determined partially by body weight (64), it would be necessary to adjust this figure for heavier Western populations. Moreover, establishment of a dietary recommendation for a nutrient must take into account individual variation in requirements through the use of an appropriate safety factor. No indication of individual variation was given in the Chinese study. However, in the case of selenium, a safety factor of 1.3 seems reasonable based on an arbitrarily assumed coefficient of variation of 15%. The coefficient of variation in a number of nitrogen balance studies carried out to estimate human protein requirements is 15% (86) and, since the metabolism of selenium is closely linked to that of protein, this estimate of variation in individual requirements seems reasonable for selenium as well. Use of this safety factor would add two standard deviations and would thereby theoretically allow the recommendation to encompass 97.5% of the population group concerned. One can then calculate a dietary selenium recommendation rounded to 70 and 55 μg/day for the standard North American 79-kg male and 62-kg female, respectively, by multiplying the Chinese estimate of the physiological human selenium requirement (40 μg/day) by the two adjustment factors (body weight and individual variation).

The above calculations establish a dietary recommendation based on saturation of a known biochemical function of a nutrient, in this case plateauing of glutathione peroxidase activity. This is a time-honored approach long used by nutritionists. This approach does not take into consideration possible beneficial effects of higher nonnutritional levels of selenium intake, an issue for further research.

CONCLUDING REMARKS

In the late 1960s both New Zealand and Finland were among the first countries in the world to approve the use of selenium as an animal feed additive to prevent economically significant deficiency diseases in their livestock. Now that the focus of selenium has shifted to human nutrition, the approaches of these two nations to the selenium problem have diverged considerably. New Zealand has consistently taken a conservative approach, with nutritionists there maintaining that ". . . there is at present no causal relationship between Se and any of the naturally occurring diseases studied except Keshan disease. . . ." (100). Authorities in Finland, however, have taken a more activist approach and, largely on the basis of epidemiological evidence, have decided to add sodium selenate to their fertilizers to increase

the selenium content of domestically produced grain (50). The objective of that national intervention was to increase the average adult dietary selenium intake above 50 μg per day, even in those years when high-selenium grain is not imported.

The controversy concerning the role of selenium in human nutrition reflects in microcosm the larger issues that are currently dividing the nutrition community. The debate between the skeptics and the believers is likely to continue until the involvement or lack of involvement of selenium (and other nutrients) in chronic degenerative diseases typically found in populations in the West is settled.

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