

The Two Faces of Selenium – Deficiency and Toxicity – are Similar in Animals and Man

L.D. Koller and J.H. Exon*

ABSTRACT

The purpose of this review article is to demonstrate the close parallelism of daily requirements, biological activity and minimum and maximum tolerable levels of selenium for animals and man. In addition, the carcinogenic/anticarcinogenic properties of selenium are discussed and a postulate of how these dichotomous effects may occur in accordance with selenium-induced immunomodulation is presented. A review of pertinent literature pertaining to the biological action of selenium in animals and man, including deficiency, toxicity, carcinogenicity and effects on immunity, is included to support these concepts.

The predominant biochemical action of selenium in both animals and man is to serve as an antioxidant via the selenium-dependent enzyme, glutathione peroxidase, and thus protect cellular membranes and organelles from peroxidative damage. The signs and symptoms of selenium deficiency closely simulate each other for animals and man. Severe deficiency is characterized by cardiomyopathy while moderate deficiency results in less severe, myodegenerative syndromes such as muscular weakness and pain as well as a variety of other selenium-associated diseases. Clinical manifestations of many of these disorders require contributory factors, such as stress, to precipitate symptoms which are documented for animals and implicated for humans. Current evidence suggests that a daily selenium consumption for man of approximately 30 μg is necessary to prevent the selenium-deficient syndrome, Keshan disease, while approximately 90 $\mu\text{g}/\text{day}/\text{adult}$ should be the

minimum daily requirement for optimum biological performance. Recognizing that humans in several countries do not meet the proposed minimum daily requirement of 90 μg , several compelling reasons are presented in deriving this minimal daily nutritional intake.

Selenosis can occur in laboratory animals, livestock, and humans following long-term exposure to selenium concentrations as low as 5 mg selenium/kg of diet (5 ppm). The selenium-induced lesions for all species are similar, which once again illustrates a positive corollary for selenium effects in both animals and man. From compilation of available data, the maximum tolerable level for selenium in man could be considered in the range of 1000 to 1500 $\mu\text{g}/\text{day}$. This is in contrast to the currently recommended maximum human tolerable level of 500 $\mu\text{g}/\text{day}$. The amount of selenium that can be tolerated, however, is dependent upon individual biological variation, nutritional status and general state of health. Therefore, individuals who consume relatively large daily amounts of selenium should periodically have their blood concentrations monitored and closely observed for symptoms of toxicity.

Selenium, once labeled as a carcinogen, is now thought to possess antineoplastic properties. Studies in our laboratory, investigating the effects of excess selenium on immunity, could possibly provide a plausible explanation for these contrasting data. Rats given selenium supplemented diets had suppressed humoral and cell-mediated immune responses but markedly stimulated natural killer cell cytotoxicity. Assuming the

immune system has a role in prevention of cancer, these data would suggest that those neoplasms which are natural killer cell-sensitive could be prevented and/or respondent to selenium therapy while those which are natural killer cell-insensitive could be augmented by selenium treatment. Further investigations are warranted to dispute or confirm this hypothesis.

The intriguing feature of selenium nutrition is the remarkable interspecies similarities of the action of this element, especially between animals and man. With few exceptions, direct extrapolations between species have a high degree of correlation. We believe that many of the long-term myths concerning selenium have been dispelled and anticipate that recognition of the biological importance, as well as limitations, of selenium nutrition will unequivocally benefit human and animal health.

Key words: Selenium, deficiency, toxicity, carcinogenicity, immunity, animals, man.

RÉSUMÉ

Cet article comporte une revue de la littérature pertinente et vise à démontrer le parallélisme étroit qui existe entre les besoins quotidiens, l'activité biologique, ainsi que les quantités tolérables minimales et maximales de sélénium, pour les animaux et l'homme. Les auteurs commentent en plus les propriétés carcinogènes et anticarcinogènes du sélénium et présentent un postulat sur la façon dont ces effets dichotomes peuvent survenir, en accord avec une immunomodulation provoquée par le

*Department of Veterinary Medicine, University of Idaho, Moscow, Idaho 83843. Present address of Dr. Koller: College of Veterinary Medicine, Oregon State University, Corvallis, Oregon 97331-4802.

Submitted April 12, 1985.

sélénium. Ils ajoutent aussi, pour supporter ces concepts, une revue de la littérature relative à l'action biologique du sélénium, chez les animaux et l'homme, y compris sa déficience, sa toxicité, ses propriétés carcinogènes et ses effets sur l'immunité.

La principale action biochimique du sélénium, tant chez les animaux que chez l'homme, consiste à servir d'antioxydant, par le truchement de la glutathion-peroxydase, enzyme qui dépend du sélénium, et à protéger ainsi les membranes et les organelles cellulaires des dommages attribuables au peroxyde. Les signes cliniques que manifestent les animaux ressemblent beaucoup aux symptômes qu'on observe chez l'homme, lors d'une déficience en sélénium. Une déficience marquée se caractérise par une cardiomyopathie, tandis qu'une déficience modérée entraîne des syndromes moins graves de dégénérescence musculaire, tels que de la faiblesse musculaire et de la douleur, ainsi qu'une variété d'autres maladies reliées au sélénium. Les manifestations cliniques de plusieurs de ces conditions requièrent des facteurs auxiliaires tels que le stress, pour accélérer l'apparition des symptômes, qui sont documentés pour les animaux et impliqués chez l'homme. L'évidence courante suggère que les humains doivent consommer quotidiennement environ 30 μg de sélénium, pour prévenir la maladie de Keshan, tandis que les adultes doivent en prendre au moins 90 $\mu\text{g}/\text{jour}$, pour réaliser une performance biologique optimale. Tout en admettant que les habitants de plusieurs pays ne consomment pas cette dose quotidienne minimale, on invoque plusieurs raisons valables pour la recommander.

L'intoxication par le sélénium peut se produire chez les animaux de laboratoire ou domestiques et chez les humains, à la suite de l'ingestion prolongée d'aussi peu que 5 mg de cet élément/kg d'aliments, i.e. 5 ppm. Les lésions attribuables à cette intoxication se ressemblent, chez toutes les espèces; ce phénomène illustre une fois de plus un corollaire positif sur les effets du sélénium, tant chez les animaux que chez l'homme. D'après la compilation des données disponibles,

la quantité tolérable maximale de sélénium, chez l'homme, se situerait entre 1000 et 1500 $\mu\text{g}/\text{jour}$. Une telle conclusion contraste avec la recommandation courante de 50 $\mu\text{g}/\text{jour}$. La quantité tolérable de sélénium dépend toutefois des variations biologiques individuelles, de l'état nutritionnel et de l'état général de la santé. Les individus qui consomment une quantité quotidienne relativement élevée de sélénium devraient donc en faire vérifier périodiquement leur teneur sanguine et il faudrait les surveiller de près, afin de détecter les symptômes d'intoxication.

On pense maintenant que le sélénium, déjà identifié comme un agent carcinogène, posséderait des propriétés antinéoplasiques. Les études relatives aux effets d'un excès de sélénium sur l'immunité, réalisées dans notre laboratoire, fourniraient une explication plausible pour ces données contradictoires. Des rats auxquels on donnait des aliments enrichis de sélénium manifestèrent une suppression de leur immunité humorale et cellulaire, en même temps qu'une stimulation marquée de la cytotoxicité naturelle de leurs phagocytes. Si on admet que le système immunitaire joue un rôle dans la prévention du cancer, les constatations précitées permettent de penser qu'on pourrait prévenir les néoplasmes sensibles aux phagocytes et/ou les amener à répondre à une thérapie à base de sélénium, alors qu'on pourrait stimuler les autres par cette thérapie. Il faudra réaliser des expériences additionnelles, pour infirmer ou confirmer cette hypothèse.

Le point intrigant du métabolisme du sélénium réside dans les ressemblances remarquables de son action chez les différentes espèces, particulièrement chez l'homme et les animaux. Sauf pour quelques exceptions, les extrapolations directes entre les espèces affichent une étroite corrélation. Les auteurs croient que les vieux mythes relatifs au sélénium ont été dissipés et ils anticipent que la reconnaissance de son importance biologique et de ses limites contribuera sans équivoque à l'amélioration de la santé de l'homme et des animaux.

Mots clés : sélénium, déficience,

toxicité, effet carcinogène, immunité, animaux, homme.

INTRODUCTION

Selenium (Se) has been recognized for years as an essential trace element for animals (1), but until recently, it has not been recognized as an essential element for man. In the United States, the regions with the lowest amounts of Se in soils and plants are the Northwest, Northeast, Southeast and areas of the Midwest which adjoin the Great Lakes (2-4). The Plains States and Southwest generally have adequate Se in soils and plants. The majority of livestock raised in low Se regions generally do not receive adequate dietary Se and thus are deficient. Extreme Se deficiency in man has been more difficult to demonstrate in the United States, primarily due to transportation of consumable products from region to region. Nevertheless, Se deficiency in man is well documented in China (5-10) while the extremely low Se content of New Zealand forages results in relatively low Se concentrations in both animal and human populations (11).

FUNCTION OF SELENIUM

The biochemistry and mechanisms of action of Se have recently been reviewed (12-14). Selenium is an important deterrent of lipid peroxidation, competes with sulfur in biochemical pathways, and is incorporated into the sulfur-containing amino acids, cystine and methionine (15-17). Selenium is incorporated into enzymes which regulate normal body processes. One Se-dependent enzyme is glutathione peroxidase (GSH-Px) (13,17,18). Glutathione peroxidase protects cellular membranes and lipid-containing organelles from peroxidative damage by inhibition and destruction of endogenous peroxides, acting in conjunction with vitamin E to maintain integrity of these membranes (13,19). Glutathione peroxidase catalyzes the breakdown of hydrogen peroxide (H_2O_2) and certain organic hydroperoxides produced by glutathione during the process of redox cycling (12,13). The toxicity of redox

cycling compounds is generally increased by Se deficiency which results in nearly a twofold increase in glutathione-S-transferase activity and glutathione synthesis in liver (20,21).

Five proteins other than GSH-Px that incorporate or require Se are the selenoprotein of muscle, selenoflagellin, Se-transport protein, and the bacterial enzymes, formate dehydrogenase and glycyl reductase (12,14). There is further evidence that Se is an essential component of nicotinic acid hydroxylase, xanthine dehydrogenase and a bacterial thiolase (12,14). Other selenoproteins and selenoamino acid transfer nucleic acids have been identified but remain undefined (14).

Selenium facilitates significant changes in metabolism of many drugs and xenobiotics. For instance, Se functions to counteract the toxicity of several metals such as arsenic, cadmium, mercury, copper, silver and lead (22). On the other hand, some metals such as tellurium and zinc are antagonists to Se and can interfere with the absorption or action of Se (23,27). Selenium has also been reported to alter cytochrome-P-450-dependent drug metabolism (28). Excess Se also results in increased synthesis of hepatic glucose-6-phosphate dehydrogenase, glutathione reductase and gamma-glutamyl-transpeptidase, thus shifting hepatic glutathione toward a more oxidized state (29). These data demonstrate the modifying effects of Se on the metabolism and toxicity of numerous xenobiotics.

SELENIUM DEFICIENCY IN ANIMALS

Selenium deficiency in livestock provokes a myriad of diseases with a potential to afflict enormous yearly economic loss to producers. These diseases range from the well recognized, ominous, severe condition of nutritional muscular dystrophy, "white muscle disease", to the numerous less explicit conditions often referred to as Se-associated or Se-responsive diseases. Some of the Se-associated/responsive diseases are characterized by muscular weakness of the newborn, unthriftiness, reduced weight gain, diarrhea, stillbirths, abortions and diminished fertility.

The commonly known Se-deficient

condition, "white muscle disease", is a myodegenerative disorder of calves and lambs (16). Affected young animals may die suddenly due to myocardial dystrophy. This form occurs more often in lambs than calves. The more common subacute form is characterized by signs of stiffness, weakness and trembling of the limbs frequently followed by the inability to stand. The muscles may tremor when the animal is forced to stand. These muscles frequently feel hard and are swollen. Involvement of the diaphragm and intercostal muscles results in dyspnea and labored breathing. The major clinical signs in calves are primarily due to involvement of skeletal muscles.

Other diseases, probably of equal importance in cattle with Se deficiency, are weakness of neonatal calves (30,31), calf scours and pneumonia (32,33), unthriftiness and reduced weight gain (16,34-36), stillbirths and abortion (16,33,37), retained placentas (38-40) and diminished fertility (16).

Many of the more subtle Se-associated conditions in sheep are similar to those observed in cattle. These include unthriftiness (16,35,36), stillborn and weak lambs (32), abortion (32), stiff lambs (16), reduced fertility (16,41,42), multiple birth and decreased wool production (32).

Several disorders in swine have been associated with Se deficiency such as nutritional myopathy, mulberry heart disease, hepatosis dietetica, gastric ulcers, diarrhea and weakness of piglets at birth (34,36,43-46).

Diseases associated with Se deficiency in the horse are more ambiguous than in other livestock. Several conditions in the equine respond to Se-vitamin E therapy including various form of myopathies such as myositis (tying-up) and polymyositis, as well as azoturia (32,47,48). Other conditions which may respond to Se-vitamin E therapy are infertility in mares, muscular weakness in foals and performance during exercise (racing, etc.) (49,52).

In poultry, exudative diathesis, encephalomalacia and muscular dystrophy in chicks are associated more with deficiencies of vitamin E than Se (19). It is interesting to note that vitamin E is required for prevention of

encephalomalacia in chicks and nutritional dystrophy in rabbits and guinea pigs, while Se prevents nutritional muscular dystrophy in goats, lambs and calves, but not in rabbits or guinea pigs. Therefore, even though Se and vitamin E complement each other in many conditions, they cannot replace one another for prophylaxis in certain specific diseases.

Stress may be an important factor required to express many of the Se-associated diseases. For example, a severe myopathy in Se-deficient yearling cattle can be precipitated by stress (exercise, transportation, etc.) (53-55). We have observed that combination of stress from cold and Se deficiency produce weakness in newborn calves. Further, since Se deficiency compromises the immune system, it is possible that additional stress may render animals more susceptible to infectious agents (See: Selenium and Immunity Section). This may be a particularly important facet to recognize since most animals are only marginally deficient in Se and clinical signs associated with Se-deficiency remain unrecognized.

DIAGNOSIS OF SELENIUM DEFICIENCY IN ANIMALS

Determination of the Se status of livestock has become markedly improved during the past few years with the discovery that Se levels in blood closely correlate with GSH-Px activity (56-63). Selenium is an essential component of GSH-Px (17,18) and is incorporated into erythrocyte GSH-Px during erythropoiesis (62). A direct relationship between blood Se concentrations and blood GSH-Px activity occurs in cattle, sheep, horses, chickens and rats.

Since as much as 98% of GSH-Px activity in peripheral blood is associated with erythrocytes (60), analysis of red blood cells for GSH-Px activity is effective for determining the Se status of animals. However, it must be kept in mind that the activity of this enzyme in erythrocytes will depend upon availability of Se during erythrocyte development (69). Therefore, erythrocyte GSH-Px activity is a relatively stable biological indicator of Se while Se analysis of whole blood, which contains both enzymatic and

nonenzymatic components, is affected by daily variations in Se intake.

Blood Se levels less than 0.05 $\mu\text{g}/\text{mL}$ (ppm) are considered as Se deficient while levels between 0.05 and 0.10 are marginal, and greater than 0.10 are adequate (63). Comparable whole blood GSH-Px levels are: deficient if less than 30 mU/mg hemoglobin; marginal if 30-60 mU/mg; and adequate if greater than 60 mU/mg hemoglobin (63,64).

SELENIUM TOXICITY IN ANIMALS

Selenium toxicity in laboratory animals and livestock has been fairly well characterized in numerous reviews and texts and will only be discussed briefly herein. There appear to be only minor variations in susceptibility to acute toxicity between species. Selenite and selenate produce similar acute toxic effects. The minimum lethal dose of selenite or selenate in rabbits, rats, dogs and cats was 1.5 to 3.0 mg/kg body weight regardless of route of administration (65,66). Signs of acute poisoning are garlicky breath, vomiting, dyspnea, tetanic spasms and death from respiratory failure (67). Histopathological lesions include congestion of the liver and kidneys, focal necrotic hepatitis, endocarditis, myocarditis and petechial hemorrhages of the epicardium (68).

Chronic toxicity studies have indicated that diets containing 5 mg/kg or more of Se result in chronic toxicity in laboratory animals (68-73). The National Academy of Sciences has accepted 5 mg Se/kg diet as the division level between toxic and nontoxic feeds (69).

Sodium selenite or naturally occurring Se fed in diets of rats at 1.6, 3.2 and 4.8 ppm for six weeks had no significant effect on growth (72). Impaired growth and increased spleen weights occurred in rats fed 6.4 ppm Se. Concentrations of 8.0 mg Se/kg feed resulted in increased mortality rates, enlargement of the spleen and pancreas, reduced liver-to-body weight ratios and decreased blood hemoglobin.

In a two year study, rats fed 0.5 ppm Se were comparable to controls while levels of 4 ppm impaired growth and reduced survivability (71). However, in another two year study when 4 ppm

Se was provided in drinking water, weight gain was equivalent for treated and nontreated controls (73). Prolonged exposure of rats to elevated levels of Se resulted in mottling and discoloration of the liver, hyperplasia and hepatic cirrhosis (71).

Livestock exhibit several manifestations of selenosis. A single dose of 2 mg Se/kg body weight administered to neonatal calves resulted in lassitude, inappetance, dyspnea and death within 12 hours following injection (74). Others have reported the minimum lethal dose of a single injection of Se to be much greater for cattle. An oral dose of 20 mg Se/kg body weight (sodium selenite) proved fatal to a calf in six hours (75), while in another study, 9.9 to 11 mg Se/kg body weight was determined to be the minimal lethal dose (76). In another study (77), 2 mg Se/kg body weight produced 100% mortality in swine within four hours of injection. A lower dose of 1.2 mg Se/kg body weight produced 100% mortality in five days. The FDA has approved Se as a feed additive for cattle, sheep, swine and chickens and permits a level of 0.1 ppm Se of the total diet (78-80). The maximum dietary tolerable levels of Se for livestock has been set at 2 ppm (1).

"Blind staggers" is a clinical expression for subacute selenosis in livestock. Affected animals exhibit impaired vision, abdominal pain, anorexia, ataxia, paralysis and death. Chronic exposure to Se results in a condition in livestock known as "alkali disease". This disorder is characterized by lack of vitality, anemia, stiffness of joints, deformed and sloughed hoofs, roughened hair coat and lameness.

In general, the minimal acute lethal dose of Se for livestock ranges from 1-5 mg/kg body weight. A diet containing 5 ppm Se for an extended period may produce signs of toxicosis while a more severe form of selenosis will occur at 10-25 ppm Se (81). The recommendation of the National Academy of Science that diets containing 5 ppm of Se or more may result in chronic toxicity in laboratory animals could also pertain to livestock.

SELENIUM DEFICIENCY IN HUMANS

It was recently suggested that Se be

considered an essential trace element for human nutrition (7,11). Selenium deficiency has clearly been associated with health problems in animals, but only recently have Se deficient disorders in man been unequivocally defined. The most prominent of these conditions, known as Keshan disease, is endemic in certain regions of China.

Keshan disease is a cardiomyopathic condition characterized by heart failure, cardiac enlargement, abnormalities of ECG, gallop rhythm and even cardiac shock. This disease is reported to occur predominately in children and women of child-bearing ages (5-10). In the early 1970s, the condition was found to be prevented by Se therapy and the high morbidity of nearly 50% was essentially eliminated (7,10). Mortality was not uncommon in severely afflicted individuals. This was the first human disease directly linked to Se deficiency and provoked the suggestion that Se be classified as an essential trace element for man (5,6,11).

The Se content of soil and foliage in New Zealand is extremely low and Se-deficient diseases are prevalent in untreated livestock. Human blood Se levels are also low but Se-deficient syndromes are not expressed unless accompanied by contributing factors such as stress. For example, a Se-responsive muscular syndrome was described in a surgical patient on total parenteral nutrition (11). Individuals with a variety of debilitating disorders also exhibited symptoms of Se-deficiency. In our studies as well as others with livestock (53-55, 82,83), we have observed that a variety of stresses may indeed precipitate expression of Se-deficient syndromes. Others have reported deficient syndromes in humans who received total parenteral nutrition (84,85). The symptoms included intermittent muscle tenderness and pain and eventual white fingernail beds. In addition, the activity of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and creatine kinase in serum was elevated.

Epidemiological studies suggest that Se deficiency may contribute to cardiovascular disease of man (86-88). The incidence of hypertensive heart disease is significantly lower in Se adequate areas of the U.S. compared

to Se deficient areas (89). Likewise, in Finland, high mortality from heart disease occurs in areas low in Se (86).

The amount of blood Se in Keshan disease patients was in the range of 0.020 to 0.026 $\mu\text{g}/\text{mL}$ (7,10). Selenium levels in the hair of afflicted individuals ranged from 0.07 to 0.12 $\mu\text{g}/\text{g}$ (7,10). Individuals in low Se areas without symptoms of Keshan disease had mean blood Se levels of 0.027 $\mu\text{g}/\text{mL}$ and Se of 0.16 $\mu\text{g}/\text{g}$ in hair (10). A human population considered to be Se-adequate had mean blood and hair Se concentrations of 0.095 and 0.36 $\mu\text{g}/\text{g}$, respectively (10). It has been proposed that a minimum adequate whole blood Se level to prevent Keshan disease is in the range of 0.03-0.04 $\mu\text{g}/\text{mL}$ with corresponding levels of Se in hair of greater than 0.2 $\mu\text{g}/\text{g}$ (7). The estimated minimum daily Se requirement to prevent Keshan disease would be approximately 30 μg (7,10). The average daily Se intake even in low Se areas was approximately three times that of the Keshan disease patients (10). This suggests that the minimum daily requirement for Se for an adult would be a minimum of 90 μg . These values approximate the minimum daily requirement recommended for animals. Although the average daily intake of Se in some countries does not meet the 90 μg level (11), lesser amounts may be sufficient for Se-dependent body functions in the absence of contributing factors such as stress. Further, vitamin E and other nutritional factors may be compensatory in regard to expression of severe Se-deficient syndromes in man.

Treatment of Se deficiency has been successful in humans (5,7,84,85). An incidence rate of 9.5-13.5/1000 of Keshan disease in endemic areas was reduced to 1-2/1000 in children treated once a week with 0.5-1 mg sodium selenite (7). In another study, intravenous infusion of 100 μg selenomethionine alleviated symptoms of selenium deficiency but was accompanied by only a small increase in plasma and whole blood Se (85). This suggests a critical point in supplementation before Se residues in blood become elevated and return to normal ranges. Similar results have been reported for Se deficient beef cattle supplemented with Se (64).

Prolonged intravenous treatment of a patient deficient in Se with 42 $\mu\text{g}/\text{day}$ elemental Se (H_2SeO_3) markedly improved both blood Se and whole blood GSH-Px activity (84). Thus, Se therapy is effective in both prevention and treatment of Se deficient syndromes in man.

SELENIUM TOXICITY IN HUMANS

The enigma surrounding toxicity of Se in man has for decades created considerable debate. Nutritionists and regulatory agencies have been perplexed in attempts to derive the no-observable-adverse-effect, lowest-observable-adverse-effect, or minimum toxic effect levels for humans. Establishment of upper limits of Se exposure for man was based either solely on animal data or a scattering of epidemiological studies in absence of appropriate experimental or quantifiable epidemiological data by which to make sound judgments. Thus, in order to protect human populations from excessive consumption of Se, 500 μg of Se was generally accepted as the maximum acceptable daily intake. However, recent information would suggest this level is unreasonably low and should be increased at least one to twofold.

A report in 1978 suggested that humans could consume 600 μg Se per day for 18 months without any adverse health effects (90). The blood Se concentration at this level of exposure was 0.62 $\mu\text{g}/\text{mL}$. A recent epidemiological study objectively quantifies the range of Se consumption, accompanied by blood and hair concentrations, which provides useful data to predict minimum and maximum levels which would result in adverse health effects in man, i.e. deficiency or toxicity (10). The report documents five levels of long-term Se consumption in man, i.e. high Se with chronic selenosis, high Se in the absence of selenosis, Se adequate, low Se and low Se resulting in Keshan disease. The daily dietary intake of Se averaged 4.99 mg/day (range 3.20-6.69) for the group with chronic selenosis. Symptoms of toxicity which developed in this group rescinded when their diets were replaced with foods which contained nontoxic amounts of Se. Individuals receiving an average daily intake of 750 μg Se did not exhibit signs of

disease. The maximum amount consumed by individuals in this group without symptoms was 1510 $\mu\text{g}/\text{day}$.

Mean blood Se levels for the five different groups were reported as high Se with selenosis - 3.2 $\mu\text{g}/\text{mL}$; high Se without selenosis - 0.44 $\mu\text{g}/\text{mL}$; Se-adequate - 0.095 $\mu\text{g}/\text{mL}$; low Se - 0.027 $\mu\text{g}/\text{mL}$; and low Se with Keshan disease - 0.021 $\mu\text{g}/\text{mL}$. The average blood concentration of Se in the high Se with selenosis group was about 30 times that of the Se-adequate group and 160 times that of the Keshan disease patients. The highest blood Se values, 7.5 $\mu\text{g}/\text{mL}$, in one individual exceeds the critical level most experimental animals can tolerate and was nearly 350 times higher than the average value (0.021 $\mu\text{g}/\text{mL}$) for Keshan disease patients.

Both hair and blood Se concentrations were reliable criteria for Se exposure, while urinary Se was variable and considered unreliable (10). The ratio of maximum tolerable level vs minimum levels to protect against Keshan disease for hair and blood were 26 and 16, respectively. However, the mean daily Se intake of adults in the high Se areas without selenosis (750 μg) was about 70 times that for the Keshan disease group.

In a separate case report described within this article (10), a 62 year old man consumed 1 mg elemental Se as sodium selenite per day for two years until development of mild signs of intoxication. The concentrations of Se in his blood and hair were 0.179 $\mu\text{g}/\text{mL}$ and 0.828 $\mu\text{g}/\text{g}$, respectively, on the day intake was discontinued.

Symptoms of Se toxicosis for man are a garlic odor of the breath, thickened and brittle fingernails with white spots or longitudinal streaks, hair that is dry, brittle and easily broken off at the scalp, red, swollen skin of hands and feet that may blister or even ulcerate, excessive tooth decay and abnormalities of the nervous system inclusive of numbness, convulsions and paralysis. Symptoms depend on severity of toxicosis.

In summary, endemic selenosis in man has occurred in areas where the average daily Se intake was 4.99 mg, while another group which received a mean daily intake of 0.75 mg (high of 1.51 mg/day) did not develop selenosis. An individual consuming 1 mg of

Se daily for two years, in addition to a normal dietary intake, developed only mild signs of toxicosis. Therefore, based on this information, it can be predicted that chronic selenosis occurs in man with a daily intake of approximately 1000 to 1500 μg of elemental Se.

CARCINOGENIC PROPERTIES OF SELENIUM

Selenium was considered to be a carcinogen for several years (70) and this notion impeded approval of Se as a feed supplement for livestock. Selenium was also unrecognized as an essential trace element for humans until recently and, consequently, interest in Se as a human nutrient waned. Nevertheless, this element was eventually recognized for its importance of maintaining health of livestock, and research progressed slowly for the next couple of decades. The advancement of technology and newly acquired knowledge of the multistep process of neoplasia in the early 1970s resulted in renewed interest in the carcinogenic action of Se. In fact, several studies indicated that Se may indeed be an anticarcinogen. A recent review (91) discusses the interactions of Se with a variety of carcinogens and illustrates the anticarcinogenic activity of Se. We will not attempt to provide a complete review of the literature herein, but rather will briefly define some of the more pertinent recent reports which describe the anticarcinogen properties of Se.

Recently, Se supplementation was shown to significantly inhibit both chemical- and virus-induced neoplasia (92-101). The development of preneoplastic lesions was shown to be very sensitive to Se-mediated inhibition (98). It has been postulated that Se inhibits the promotion phases of carcinogenesis (107). Upon withdrawal of the Se supplementation, tumors will emerge at the same rate as those in Se-untreated animals (97,99,102-104).

It has been suggested that Se protects against oncogenesis by inhibiting metabolic activation of carcinogens (105,106) but this mechanism remains unconfirmed (92). Another study (107) concluded that Se can inhibit both the initiation and promotion phases of carcinogenesis and that a continuous intake of Se is necessary to achieve maximum inhibi-

tion of tumor genesis. The effect of Se on immune function may further complicate the issue of Se carcinogenicity/anticarcinogenicity and will be discussed in the following section of this article.

There is no evidence that Se is carcinogenic in humans. In fact, epidemiological data would suggest that Se may indeed protect against human cancer. An increased incidence of colorectal, breast and other cancers in humans occurred in geographic regions deficient in Se (108,109). Further, the blood Se levels in humans who developed cancer during a five year period were significantly lower than were those for matched control subjects (110). Low Se levels were associated primarily with cancer on the gastrointestinal tract and prostate. Thus, recent information would dispel that Se is a carcinogen and actually suggest that Se is a potential and perhaps formidable anticarcinogen. Controlled investigations, particularly those relevant to man, are warranted to validate and characterize the antineoplastic properties of Se.

SELENIUM AND IMMUNITY

The functioning immune system requires adequate levels of Se for optimum performance. Selenium augments immunity and has a role in inflammation. Animals deficient in Se and vitamin E had lower antibody titers in response to vaccination than did nondeficient animals (111). Excess Se potentiated the protective effect of a killed vaccine (112). Selenium has been reported to enhance antibody synthesis, thereby amplifying the immune system in response to antigenic stimulation (112-116). Selenium deficiency impaired mitogenic stimulation of lymphocytes in both dogs (111) and mice (117). These data are indicative of the sensitivity of the humoral immune system to the presence of Se for normal function. Very little information is available to indicate the influence of Se on cell-mediated immunity in animals.

As mentioned previously, Se is a component of the active site of the enzyme, GSH-Px. A substrate for this enzyme is hydrogen peroxide (H_2O_2) which is generated during the oxidative processes, including the oxidative

burst of phagocytes (118). Accumulation of H_2O_2 and other peroxides or oxygen radicals can result in self-destruction of a cell and have been implicated as nongenotoxic mediators of neoplasia.

Neutrophils, peritoneal macrophages and pulmonary alveolar macrophages from Se-deficient animals have low amounts of GSH-Px activity and decreased microcidal activity (119-124). Further, the phagocytic capability of neutrophils was not diminished, but the ability of these cells to destroy the phagocytized bacteria was compromised (121,124). Evidence has been presented that Se-deficient neutrophils have decreased superoxide dismutase-sensitive reduction of both cytochrome C and 2-(p-iodophenyl)-3-(p-nitrophenyl)-5-phenyl tetrazolium chloride (INT) and, thus, diminished ability to produce superoxide radicals (O_2^-) required for microbial activity. In fact, it has been proposed that peroxide-mediated cell injury could also account for the reduction in lymphocyte mitogenesis and enhancement of adjuvant arthritis in animals (117). A dearth of information is available for Se-associated immune function in humans. However, one study indicated that granulocytes from Se-deficient individuals had a lower cytotoxic capacity than did granulocytes from Se-supplemented individuals (125). Other immune parameters examined were unaffected.

In our laboratory, we have observed that excess dietary Se will significantly ($P \leq 0.05$) stimulate natural killer cell (NKC) cytotoxicity and concurrently suppress both cell-mediated and humoral immune responses in rats (126). The delayed-type hypersensitivity response was suppressed in rats fed 0.5, 2.0 or 5.0 ppm Se for ten weeks while the humoral immune response was only impaired at the highest dose (5.0 ppm). The high dose would be considered near toxic levels in the rat under prolonged exposure. Conversely, the NKC activity was enhanced at 0.5 and 2.0 ppm with no effect occurring at the 5.0 ppm Se level. The effect of Se treatment on prostaglandin E_2 (PGE_2) and interleukin 1 activity of macrophages was also assessed. Prostaglandin E_2 activity was significantly reduced at the

highest dosage of Se while interleukin 1 production was unaffected.

Immune surveillance of neoplasia requires a variety of cells often working together in an interrelated network which are intricately regulated by numerous immunocytokines. Different types of cancer may be sensitive to a particular immunocyte population(s) such as cytotoxic T cells, while others may be controlled more by macrophages or NKC. Recent information favors the NKC as the primary effector of immune surveillance, keeping in mind that not all tumor cells are NKC sensitive. Nevertheless, the NKC serves as a model system to assess the development, progression, regression as well as prognosis for many types of tumors.

It can be postulated from immune studies recently completed in our laboratory (126) that perhaps the marked enhancement of NKC activity could be considered a mechanism underlying the anticarcinogenic properties of Se. Thus, neoplasms that are NKC sensitive could be prevented and/or respondent to Se therapy. On the other hand, those neoplasms that are not NKC sensitive could actually be augmented since excess Se impaired both humoral and cellular immunity. This hypothesis remains to be tested.

SELENIUM-ASSOCIATED SIMILARITIES OF ANIMALS AND MAN

A comparison of Se requirements of animals and man is not available in the literature. The intention of this section is to demonstrate the parallelism which occurs in regard to Se function, deficiency, toxicity, lesions and other factors in man versus animals. The data from which this information was extracted will, with an occasional exception, demonstrate that data derived from animal studies can be directly extrapolated to humans with predictable precision.

The pharmacokinetics and biochemical actions of Se are comparable for man and animals. The predominant function of Se as an antioxidant is mediated through the action of the Se-dependent enzyme, GSH-Px, which activates several biological processes such as superoxide dismutase. Selenium also synergizes the action of vitamin E and facilitates

metabolism of many drugs and xenobiotics.

Severe Se deficient syndromes are expressed similarly in animals and humans. An example is the cardiomyopathy-associated condition in young livestock described as "white muscle disease". A comparable syndrome in humans is Keshan disease. The cardiomyopathy occurs predominantly in children and mimics both the lesions and age of the disease in livestock.

A counterpart of Se-associated diseases in animals occur in man, particularly following stressful situations such as surgery or in association with debilitating diseases. For instance, a Se-responsive muscular syndrome has been described in surgical patients (11). These data would suggest that the stress of surgery in Se-marginal humans may precipitate syndromes similar to those reported for Se-marginal animals.

Diets which contain less than 0.1 ppm Se (100 μg Se/kg feed) are considered as inadequate and deficient for livestock. Blood Se concentrations of less than 0.05 $\mu\text{g}/\text{mL}$ are regarded as Se-deficient in animals, while levels between 0.051 to 0.075 are low marginal, 0.076-0.10 marginal, and greater than 0.10 adequate. Glutathione peroxidase provides a positive correlation to Se for diagnostic purposes (63). The values representative of Se status in humans are less clearly demarcated, probably due in part to a more varied source of Se in the diet. However, the evidence discussed previously strongly suggests that a daily Se requirement of approximately 30 μg Se is necessary to prevent the Se-deficient syndrome, Keshan disease, in man and that at least 90 $\mu\text{g}/\text{day}$ is the minimum daily requirement. The recommended minimum daily requirement of Se may be greater than that previously proposed for several reasons. First, the data collected from human studies in China ranging from severe Se deficiency to toxicity, indicated that the average Se content of cereals grown in low Se areas was approximately two to three times that in areas where Keshan disease patients resided (10). Second, although the average daily intake of Se by humans in some countries is less than the 90 μg proposed as a minimum

daily requirement, a lesser amount may be insufficient for optimum function of certain biological systems when provoked by contributory factors such as stress. This does indeed occur in animals and has been documented for man. Third, the overall nutritional status of a given demographic population may either predispose, or conversely, partially compensate for low Se intake. For instance, an individual low in vitamin E may require more Se than an individual with high levels of vitamin E. This is exemplified by what appears to be a species specific, myodegenerative, Se-deficient-like syndrome which occurs in sheep deficient in vitamin E, but possess adequate levels of Se (127). Fourth, there is compelling evidence in both laboratory animals and livestock that marginal levels of Se may impair optimum function of complex biological systems such as the endocrine and immune systems. Further knowledge must be acquired to better delineate these relationships. Finally, the narrow margin between minimal daily requirement and maximum tolerable levels has been a deterrent for physicians to recommend Se treatment. Expansion of this margin as proposed herein would reduce the concern of toxicosis due to prescribed supplementation.

It would appear from data accumulated from human studies and considering the factors discussed above that blood Se concentrations of less than 0.03 $\mu\text{g}/\text{mL}$ represent severe deficiency, 0.03-0.04 $\mu\text{g}/\text{mL}$ low marginal, 0.04-0.075 $\mu\text{g}/\text{mL}$ marginal and greater than 0.075 $\mu\text{g}/\text{mL}$ adequate. These levels are slightly lower than those designated for equivalent categories for livestock.

Chronic Se toxicity will occur in laboratory animals and livestock fed diets containing 5 mg/kg of Se. A similar exposure to Se (4.99 mg/kg) resulted in chronic selenosis in man (10). The lesions of selenosis for both animals and man are similar as characterized by abnormalities of the hooves/nails, hair and skin, as well as the central nervous system.

The information available on which to base a recommended maximum tolerable daily consumption of Se for humans is sparse but compelling. A lower limit, dependent upon individ-

ual biological variation and total nutritional status, as well as other factors can be established. The group of individuals in China (10) classified as high in Se, but without clinical signs of toxicosis, had a mean daily intake of 750 μg Se with a maximum of 1510 μg /day. In the same study, long-term daily consumption of 3.2 to 6.69 mg Se resulted in selenosis. In another report, a man who consumed a daily supplement of 1 mg Se for two years, in addition to normal dietary Se, eventually developed minor symptoms of toxicosis which were reversible. These data taken together would suggest that the maximum tolerable level for Se in man should be from 1000 to 1500 μg /day. Once again, individual biological variation and total nutrition as well as other factors would predicate the actual amount of Se resulting in toxicosis following prolonged exposure. Nevertheless, individuals who consume large daily amounts of Se should periodically monitor blood Se levels and closely observe for symptoms of toxicity.

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