Selenium in Ruminant Nutrition: A Review

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ABSTRACT

The early interest in selenium related primarily to its toxicity, but since 1957 the element has been recognized as a dietary essential. The dietary requirement for selenium by most species is about .1 ppm. Deficiencies of selenium in cattle and sheep have been confirmed under natural grazing conditions in many countries of the world. Overt signs of inadequacy such as white muscle disease (nutritional muscular dystrophy) occur primarily in young calves or lambs born to selenium deficient dams. Infertility has increased in ewes grazing pastures low in selenium. In general, signs of deficiency have not occurred in older animals such as finishing beef cattle and lactating dairy cows. Subclinical deficiencies of selenium are not determined easily, however, and thus an inadequacy of the element may be limiting maximum animal performance under certain circumstances of drylot feeding. The current nutritional status of ruminant animals in many geographical areas and involving various feeding programs with this element has not been established. The recent widespread deficiency problems with nonruminants suggest that such an assessment should be made. Concentration of selenium in tissue, particularly in the liver, has been used in establishing selenium status of the animal. With lambs glutathione peroxidase activity in certain tissues may be a more accurate indicator of selenium adequacy than is selenium content of the tissue. Supplemental sodium selenite and sodium selenate by either oral administration or parenteral injection have prevented clinical signs of selenium deficiency and animal losses in both ruminant and nonruminant animals. Heavy pellets containing elemental selenium for placement in the rumen have proved effective. In general, organic forms of selenium are absorbed more readily by animals than are inorganic compounds. The dietary requirements for selenium and its metabolism are influenced by many nutrient interrelationships, including its interactions with sulfur, lipids, vitamin E, proteins, amino acids, and several microelements. The Food and Drug Administration gave approval in 1974 for the oral administration of supplemental selenium as either sodium selenite or sodium selenate to certain classes of swine and poultry. Similar approval in the United States for ruminants will require additional information, particularly with regard to the influence of dietary intake on concentrations of selenium in tissue and milk in beef and dairy animals.

INTRODUCTION

Our purpose is to evaluate recent developments in research with selenium as they relate to ruminant nutrition. Several reviews of research with selenium have been published (1, 30, 31, 65, 70, 100, 102, 116, 138). Except for providing a brief history, or a basis for specific discussion, reference will not be made to these earlier reviews.

TOXICITY

Perhaps more than any other mineral element currently considered to be essential for animals, selenium has had a profound and lengthy history of toxicity. This history as a toxic element undoubtedly has influenced thinking about selenium as a dietary essential. The toxicity of selenium to domestic animals (110, 116) and humans (17) has been reviewed. Rosenfeld and Beath (116) provide quotes from the writings of Marco Polo suggesting that he...
encountered problems of selenium toxicity in “beasts of burden” during his travels through western China about 1295. The same authors refer to a report written in 1857 by T. C. Madison, an army surgeon, in which Madison describes conditions in cavalry horses at Fort Randall, South Dakota that eventually resulted in the sloughing of hooves, mane, and tail. This condition or disease, termed “alkali disease” or “blind staggers,” resulted in extreme losses of livestock in a number of western states. It was not until 1934 that selenium was identified as the causative toxic agent (28). Emphasis on the toxicity of selenium continues to the present time. Galston (32), writing in a recent publication of the American Museum of Natural History, discussed many of the adverse effects of selenium and the possible danger of the element to human health. That selenium is considered to be a metabolically essential element, however, was not mentioned.

**ESSENTIALITY**

Selenium has been considered an essential element since Schwarz and Foltz (123) demonstrated in 1957 that it was the effective component of “factor-3” (120) in preventing liver degeneration in rats. Soon after, selenium was shown to prevent exudative diatheses in chicks (112, 122) and nutritional muscular dystrophy in calves (99) and lambs (64). Further studies with selenium involving other species and other deficiency syndromes against which selenium and/or vitamin E may be effective have been reviewed (30, 31, 70, 102, 133, 138).

**REQUIREMENT**

The dietary requirements and ppm of selenium toxic for domestic animals as summarized by the National Research Council are in Table 1. Values for swine and poultry are presented in addition to those for ruminants for comparative purposes. Whether the animal is a ruminant or nonruminant, it generally is considered that its selenium requirement will be satisfied by .1 ppm of the element in the diet. A higher .2 ppm, however, has been established as the requirement for turkeys. Interpretation of available data has resulted in wide ranges for toxic amounts of selenium for certain species. Even so, the widest range of 3 to 20 ppm set for sheep yields a minimum toxic-to-required ratio of 30, indicating a greater margin of safety with selenium than occurs with copper, for example.

**SELENIUM IN FEEDSTUFFS**

Distribution of selenium in forages and grains in various areas of the United States is in Fig. 1. The most selenium deficient regions include the Northwest, Southeast, and Northeast, including many of the states adjoining the Great Lakes. In regions bordering these areas, approximately 50% of the forages or grain samples contained .1 ppm or more of selenium. In an area bounded by the Rocky Mountains to the west and the Mississippi River to the east, grains and forages were generally adequate (>1 ppm) in selenium. Values for selenium in corn samples representing several regions of the United States are in Table 2 (137). Highest selenium was in corn grown in the Dakotas and Nebraska with lower concentrations in corn produced in states east of this area. Research by Hoffman et al. (65) in Canada showed that selenium in tissues from lambs and calves generally was lower in the eastern area and higher in the central to western portion of the country. Thus, the geographic pattern in the distri-

<table>
<thead>
<tr>
<th>Species</th>
<th>Reference</th>
<th>Selenium (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy cattle</td>
<td>103</td>
<td>.1</td>
</tr>
<tr>
<td>Beef cattle</td>
<td>101</td>
<td>.05 to .1</td>
</tr>
<tr>
<td>Sheep</td>
<td>106</td>
<td>.1</td>
</tr>
<tr>
<td>Swine</td>
<td>105</td>
<td>.1</td>
</tr>
<tr>
<td>Chickens (0 to 8 wk)</td>
<td>104</td>
<td>.1</td>
</tr>
<tr>
<td>Turkeys (0 to 8 wk)</td>
<td>104</td>
<td>.2</td>
</tr>
</tbody>
</table>

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Low - approximately 80% of all forage and grain contain < .05 ppm of selenium.

Variable - approximately 50% contains > .1 ppm.

Adequate - 80% of all forages and grain contain > .1 ppm of selenium.

Local areas where selenium accumulator plants contain >50 ppm.

FIG. 1. Regional distribution in the United States of forages and grains which are low, variable, adequate, or toxic in selenium. Prepared by Kubota and Allaway (77).

TABLE 2. Selenium concentration in corn originating in various areas of the United States.a

<table>
<thead>
<tr>
<th>Origin</th>
<th>No. of samples</th>
<th>Range (ppm)</th>
<th>Mean (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan</td>
<td>17</td>
<td>.01 – .09</td>
<td>.03</td>
</tr>
<tr>
<td>Indiana</td>
<td>17</td>
<td>.01 – .15</td>
<td>.04</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>5</td>
<td>.02 – .13</td>
<td>.04</td>
</tr>
<tr>
<td>Illinois</td>
<td>31</td>
<td>.02 – .15</td>
<td>.05</td>
</tr>
<tr>
<td>Iowa</td>
<td>25</td>
<td>.02 – .16</td>
<td>.05</td>
</tr>
<tr>
<td>Missouri</td>
<td>4</td>
<td>.02 – .09</td>
<td>.05</td>
</tr>
<tr>
<td>Minnesota</td>
<td>23</td>
<td>.02 – .19</td>
<td>.09</td>
</tr>
<tr>
<td>North Dakota</td>
<td>5</td>
<td>.09 – .26</td>
<td>.19</td>
</tr>
<tr>
<td>Nebraska</td>
<td>6</td>
<td>.04 – .81</td>
<td>.35</td>
</tr>
<tr>
<td>South Dakota</td>
<td>9</td>
<td>.11 – 2.03</td>
<td>.40</td>
</tr>
</tbody>
</table>

aFrom a summary by Ullrey (137).
bution of selenium apparently is similar in the United States and Canada.

In research cited by Ullrey (137), 20 different corn hybrids grown in the same location in Michigan had an average selenium content of .014 with a range of .007 to .024 ppm (dry basis), suggesting differences in the capability of various hybrids to concentrate selenium in the grain. Effect of location was pronounced in the same study when a single hybrid grown in 17 locations within the state yielded in the grain an average of .003 and a range of .013 to .089 ppm selenium on a dry matter basis.

Selenium content of plants is influenced by plant species, chemical form, and quantity of the element in the soil, and other soil related factors (78, 102).

DETECTION OF DEFICIENCY

Signs of a pronounced dietary selenium deficiency in ruminants include reduced growth and white muscle disease (nutritional muscular dystrophy) in young animals and poor reproductive performance in older animals (41, 102, 138). When such signs of deficiency become evident, however, losses of economic importance already have occurred. It is of value to have a means of assessing the selenium status of animals without depending on the expression of overt signs of selenium deficiency. Concentration of selenium in various tissues, including liver, kidney, heart, and muscle, fluctuates with dietary intake of the element, and results from several studies have been summarized (102). Andrews et al. (4) indicated that 1.0 ppm in the kidney cortex and .1 ppm or more in the liver (fresh basis) are indicative of adequate selenium in sheep. These authors suggest that .05 ppm selenium in the liver (fresh basis) is borderline and that .02 ppm represents a severe selenium deficiency.

Oh et al. (108) have reported that measurement of tissue glutathione peroxidase, an enzyme containing selenium, may be useful in establishing selenium status of the animal. With lambs, amount of this enzyme in serum increased with additions of selenium to a basal diet containing .01 ppm selenium and plateaued with .1 ppm added selenium. Response of enzyme was similar for muscle and heart tissue, but for pancreas and erythrocytes, the content continued to increase with added selenium. Maximum growth and feed efficiency were obtained with addition of .05 ppm Se.

In studies with sheep, Godwin and Fraser (39) and Godwin (36, 37) have shown that subclinical cases of nutritional muscular dystrophy can be detected by electrocardiography. Confirmation of the condition was by slaughter of young sheep and lambs which had shown abnormal electrocardiograms. Rosenfeld and Beath (116) suggested that muscular dystrophy affects both skeletal and cardiac muscle in lambs and calves, with a predominance of skeletal muscle damage in lambs while in calves cardiac muscle degenerates most frequently.

SUPPLEMENTATION

Injectable preparations of selenium-vitamin E combinations have been used for ruminants under veterinary supervision for several years. Except for obtaining grains or other feeds from areas of the country where higher selenium is found normally, injection has been the primary means in the United States of providing selenium for ruminants. Feeding supplemental selenium has been approved for certain nonruminants. On February 7, 1974, an order of the Food and Drug Administration (119) became effective allowing .1 ppm supplemental selenium as either sodium selenite (Na2SeO3) or sodium selenate (Na2SeO4) to be fed to all classes of swine and to chickens 0 to 16 wk of age. A supplementary .2 ppm selenium was allowed for all classes of turkeys. Similar approval for the use of oral supplemental selenium for ruminants will require additional data particularly with regard to selenium accumulation in the tissues of beef animals and excretion in the milk of dairy cows.

BIOAVAILABILITY

Responses have been positive in grazing ruminants with oral or injected supplemented selenium as either sodium selenite or sodium selenate (35, 70, 100, 138). Preventive oral doses of inorganic selenium salts in amounts of 5 mg for adult sheep or 1 to 2 mg selenium for lambs during the first few weeks of life were effective in Australia and New Zealand. Four doses proved sufficient in practice (35). Paulson et al. (113) used sodium selenate in trace mineralized salt which was offered ad libitum to pregnant and postpartum ewes at 26, 132, and 264 ppm selenium in the mixture or
equivalent to .15, .90, and 1.80 ppm selenium in the diet. The smallest amount was effective in preventing nutritional muscular dystrophy (NMD) in lambs. The basal diet contained about .1 ppm selenium.

Physical characteristics of the two selenium salts are similar to sodium chloride and mix uniformly (70). Selenate was thought to be preferable, however, because selenite is more readily reduced to less available elemental selenium which could form insoluble compounds with other metals. The stability of sodium selenite in several premixes was observed after storage (44). With carriers of corn meal, wheat flour, salt, or calcium carbonate, odor or color were unchanged. With a glucose premix, changes were found within 1 mo, and with cornstarch or sucrose, within 3 to 12 mo. The odor was musty and sweetish and certain particles changed from white to pink or red in these premixes. Selenium retention in pigs fed the stored glucose-selenium premix tended to be lower than in pigs fed a fresh preparation. A recent report indicated that either selenate or selenite in a variety of premixes would be stable when kept dry at reasonable temperatures (5).

Since supplementation of ruminant diets with selenium salts has not been permitted in the United States, incorporation of high-selenium grains into mixed feeds for selenium-deficient areas has been practiced, but monitoring of final selenium concentrations has not been feasible. Water-soluble, organically-bound selenium is superior to all other selenium compounds in bioavailability to plants or animals and is also the least toxic form of the element (116). In crop plants, the percentage of the organic selenium which was water soluble ranged from approximately 30 to 60%. None of the plant selenium was in a selenate or selenite form.

Injections of selenium and/or vitamin E have been used in many countries when needed. In the United States, the combined injection has given good results under field conditions for a number of years (98). Injections, however, are time consuming and expensive. For these reasons, their use has been limited primarily to therapy rather than as a preventive measure. The latter would require a continuous low dosage supply to the animal of selenium and/or vitamin E.

Australian workers have investigated the use of intraruminal selenium pellets in grazing sheep. Heavy pellets made of 1 g elemental selenium and 9 g iron were well retained and free of calcium phosphate coating (79). Selenium was being released to the sheep, and concentrations of the element in edible tissues were similar to those in normal animals after 6 or 12 mo. Handreck and Godwin (46) studied the availability to sheep of selenium pellets labelled with $^{75}$Se. The pellets were calculated, on the basis of tissue and excretory analyses, to release about 1 mg selenium daily, and blood and tissue selenium were within normal limits. Godwin (42) reported that lambs fed a selenium-deficient ration until signs of NMD appeared recovered after introduction of ruminal selenium pellets. With grazing beef cows on selenium-deficient pastures, 30 g pellets (10% Se, 90% Fe) increased selenium of blood within 5 wk comparable to animals which had received a selenite drench (43). Lee (81) reported that, in some experiments, when as many as three heavy pellets (Se, Co, and steel grinder) were in the rumen simultaneously, the selenium pellets were well retained with the loss of only one selenium pellet per 40 or 50 animals in 1 yr. The presence of a steel grinder pellet increased the release of selenium (82).

Canadian workers (70) investigated the use of slow-release vitamin E and selenium pellets in ewes and lambs for control of NMD. Sodium selenite pellets were implanted in the loose connective tissue behind the shoulder in pregnant ewes or in lambs which were fed dystrophy producing hay. Pellets containing 20 mg selenium as sodium selenite with stearic acid and silastic glue were implanted in ewes 49 to 78 days (mid-gestation) prior to lambing, or pellets containing 10 mg selenium as sodium selenite with hydrogenated peanut oil and magnesium stearate were placed in ewes 1 to 15 days (late gestation) before lambing (48). Hay containing approximately 15 ppb selenium and 15 ppm tocopherol was sprayed with a urea-sucrose mixture and fed to all animals, including an untreated group. Both implantation treatments increased blood selenium in the lambs and ewes two to four times that of untreated animals. Milk selenium at 1, 60, and 90 days of lactation was 9.5, 7.2, and 8.0 ppb, respectively, for untreated animals and averaged 25, 15.4, and 10.6 ppb, respectively, for the treated ewes. Lamb muscle pathology was
reduced with selenium treatment of ewes. In a similar experiment (53), NMD was prevented completely without supplementary selenium in vitamin E-implanted ewes or lambs, suggesting that the lamb’s requirement for selenium was reduced with adequate vitamin E. Selenium implantation was completely effective even when lambs were receiving relatively low vitamin E in the milk. Godwin (37), however, concluded that dietary vitamin E plus 10 mg selenium administered as a drench every 2 wk to gestating ewes did not increase tissue selenium in the lambs to concentrations above those for lambs from ewes receiving only selenium. The 10 mg selenium drench every 2 wk maintained normal blood selenium in the ewe while a single drench of 50 mg selenium before mating raised blood selenium for 2 to 3 mo but did not result in increased selenium concentrations in milk. Selenium concentrations were normal in edible tissues of lambs from implanted (70) and drenched (37) ewes.

Implantation of selenium pellets into neonatal beef calves born to cows fed selenium-deficient rations (58) also was effective in preventing NMD. Pellets containing 15 mg selenium as sodium selenite with stearic acid and silastic acid as vehicles were placed in the subcutaneous tissue at the base of the ear. One month after implantation no trace of the pellet remained, and a hole was in the conchal cartilage. Plasma selenium of implanted calves was higher than of controls and within normal range. Nutritional muscular dystrophy and elevated serum glutamic oxaloacetic transaminase content resulted in several of the nonimplanted calves but not in the implanted calves.

Canadian authors have suggested that the use of selenium-fortified salt, blocks, or mineral mixtures appears to be the most promising procedure for prevention of ruminant NMD resulting from a deficiency of selenium and/or vitamin E. A selenium and vitamin E fortified mineral supplement was fed to selenium-deficient rations (58) also was effective in preventing NMD. Pellets containing 15 mg selenium as sodium selenite with stearic acid and silastic acid as vehicles were placed in the subcutaneous tissue at the base of the ear. One month after implantation no trace of the pellet remained, and a hole was in the conchal cartilage. Plasma selenium of implanted calves was higher than of controls and within normal range. Nutritional muscular dystrophy and elevated serum glutamic oxaloacetic transaminase content resulted in several of the nonimplanted calves but not in the implanted calves.

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that organically bound dietary selenium produced higher tissue selenium than supplemental selenium fed as sodium selenite when both provided .44 ppm selenium in the diet. The addition of .1 ppm selenium as sodium selenite to a diet naturally high in selenium did not contribute significantly to tissue selenium. Results were similar for Jenkins and Winter (73) using sodium selenate to add .1 ppm selenium to diets containing .46 and .78 ppm natural selenium. The authors suggested that rapid urinary excretion of the inorganic sources could explain the differences in retention by nonruminants of organic and inorganic dietary selenium. However, Thomson and Stewart (135), in studies with rats on the utilization of $^{75}$Se selenomethionine and $^{75}$Se selenite, indicated that $^{75}$Se from both sources was metabolized similarly when administered either orally or intravenously and ultimately was incorporated into the same metabolic pool.

Selenium retention and tissue distribution in rats with different forms of selenium supplemented comparably with low-selenium corn and Torula yeast diets indicated that apparent selenium retention was greater with dietary selenomethionine at .12 ppm selenium than from dietary selenite at .146 ppm selenium but no differences in retention at less than .1 ppm selenium in the diet with either source (11). Muscle selenium was higher with high selenomethionine than high selenite, but selenium in other tissues was related more to selenium from diet than to source. There were no differences between sources in maternal transfer of selenium to the young.

Chen (14) studied effects of dietary sources of selenium in vivo and in vitro on liver lipid peroxidation in rats with and without vitamin E. Selenium 1 ppm was added as selenomethionine, selenocystine, or sodium selenite. The latter was as effective as vitamin E at 15 IU/kg of diet in reducing lipid peroxidation, and the three selenium compounds were similar in effectiveness. In vitro, however, methionine, selenomethionine, and selenocystine improved tissue antioxidant status of vitamin E deficient liver homogenates while vitamin E, sodium selenite, glutathione, and ascorbic acid did not.

**METABOLISM**

Metabolism of absorbed selenium appears to be similar for ruminants and nonruminants. Because a portion of dietary selenium becomes incorporated into microbial material, the major excretory pathway for oral selenium is fecal in ruminants and urinary in nonruminants under most conditions. With toxic selenium circumstances, pulmonary excretion assumes increasing importance (88).

There is considerable evidence that the oxidation state of selenium tends to be reduced during metabolism in contrast to sulfur which generally undergoes oxidation (34). Ehlig et al. (22) found higher tissue selenium retention by lambs fed selenomethionine than by those fed selenite. However, excess methionine inhibited in vitro incorporation of $^{75}$Se selenomethionine into rumen microorganisms (142). The effects of various forms of sulfur on in vitro uptake of $^{75}$Se by rumen microorganisms from both $^{75}$Se selenite and $^{75}$Se selenomethionine have been studied. Both cysteine and methionine reduced uptake of $^{75}$Se by rumen microorganisms from $^{75}$Se selenomethionine to a greater extent than from $^{75}$Se selenite. The $^{75}$Se uptake was not different with sulfate, sulfite, or sulfide. Effects of dietary sulfur in vivo, however, on the protective effects of selenium have not been consistent, and the author suggested that sulfur status of the animal might influence selenium metabolism in ruminants. Uptake of $^{75}$Se by rumen microorganisms in vitro was related inversely to selenium and vitamin E status of sheep (47, 144).

Only a minor amount of $^{75}$Se, administered intraruminally as selenomethionine, traversed the rumen wall to blood of sheep (50). The authors calculated that of the total administered dose, at 3 h post dosing, .05% was in the total blood volume, 2% in the total muscle mass, .14% in the liver, and .05% in the kidneys. Previously (146) $^{75}$Se, as selenite or selenate, essentially was unabsorbed from the rumen, slightly absorbed from the abomasum, and secreted into duodenum and jejunum with net absorption in the lower portion of the small intestine. Results with organic salts were similar when the liquid phase of digesta in sheep was examined following oral and intravenous dosage of $^{75}$Se selenomethionine (51). The authors suggested that selenium in the liquid phase was largely protein bound and that following hydrolysis of the microbial cell protein, the element was absorbed, like sulfur, as
In the young preruminant lamb or calf, selenium deficiency exerts damaging effects more frequently than in the older animal. With development of the rumen, afflicted animals may recover from NMD (142). The utilization of dietary selenium in milk by lambs and their dams was investigated with both inorganic and organic dietary Se (69). Radioactive selenium as selenite and selenomethionine was distributed differently in the milk proteins of ewes. The organic form produced milk selenium which was more available to lambs although milk and tissue selenium was higher in dams fed selenite. Results were similar when bovine skim milk of high natural selenium content and of low selenium content plus sodium selenite to equalize selenium was fed to rats and chicks (89). Franke et al. (29) found no influence of increased milk selenium on milk tocopherol or on reduction of oxidized milk flavor when cows were given the equivalent of 5 ppm selenium as sodium selenite either orally or by subcutaneous injection. Supplementation of the ration with tocopherol or ethoxyquin, however, increased oxidative stability of milk (21). Selenium concentration in milk varies widely within animal groups and geographical areas and is influenced by processing. Mean selenium for dairy products analyzed by Morris and LeVander (97) was 69 ppb, on a fresh weight basis. Whole homogenized milk contained 12 ppb selenium, with cheeses about ten times and cream about one-half that concentration. Other selenium concentrations for bovine milk were 5 to 67 ppb by United States authors (89, 107), 49 to 67 ppb and 5 to 13 ppb by New Zealand authors (45, 92, 96), and 3 to 21 ppb by Canadian authors (72).

Hoffman et al. (63) summarized selenium concentrations of muscle and kidney in calves and lambs in the United States, Canada, and New Zealand. Selenium of lamb tissue was positively related to selenium in the diet of the ewe, particularly with deficient diets where selenium concentrations of muscle and kidney cortex were below .5 and 5 ppm, respectively, on a dry matter basis. Additionally, there appears to be a requirement for available vitamin E in milk to provide for the effective utilization of selenium by the young ruminant (70). Selenium passes through the placenta to the rat fetus (90, 128). Fetal loss due to embryonic or neonatal death has been reduced in ruminants by administration of selenium and/or vitamin E to pregnant females in geographical areas of congenital NMD (70).

Selenium is attached firmly to all types of protein following absorption, but whether protein synthesis is required for attachment is not yet clear (88). In plant and animal metabolites selenium has been related intimately to sulfur-containing components, and the two elements may utilize the same metabolic pathways (91, 142). Since no known biochemical pathway has been identified in nonruminant animals for reduction of inorganic sulfate and biosynthesis of sulfur amino acids, the possible biosynthesis of inorganic selenium into selenoamino acids has been questioned (140, 142).

Any reduction of selenium administered to animals in the higher oxidation states which could occur in vivo would produce selenium metabolites far less toxic within the animal than selenite or selenate (88). Generally, selenium has been thought to be metabolized by incorporation into isologues of the sulfur amino acids, and particularly into methionine (91). Jenkins (67) found that none of the selenium derived from orally administered selenite in chick serum proteins was either selenomethionine or selenocystine and suggested that the majority of the selenium was covalently bound between the sulfurs of half-cystine polypeptide residues and could be released by nonproteolytic means. If so, protein incorporation and release of selenium would not be dependent on protein synthesis or catabolism. Recent studies with rabbits and rats (9, 40) generally confirm the results with chicks but suggest that a small portion of selenium may be incorporated during protein synthesis and that perhaps the excess absorbed selenium may be bound as a trisulfide. Selenium can be eliminated via the lungs under certain conditions of excess dietary intake. Results derived from studies of selenium metabolism, therefore, appear dependent on the intake of selenium relative to the requirement for the element.

Ganther and Hsieh (33, 34) have proposed the conversion of selenite to organoseleno compounds according to scheme [1] where GSH is glutathione, GSsSG is selenodiglutathione.
one, SAM is S-adenosylmethionine, and (CH$_3$)$_2$Se is dimethyl selenide. Anaerobic conditions favored reduction of selenium.

Diplock (19) has further refined this proposal to include the vitamin E effect and a selenium detoxification mechanism, according to scheme [2] where $a$ is dimethyl selenide, a volatile metabolite, and $b$ is trimethyl selenide ion, a urinary metabolite, and methylation provides a detoxification mechanism; and where $c$ is a possible antioxidant effect of tocopherol in maintaining the reducing environment for incorporation of protein selenium.

Hoekstra (61) proposed Scheme [3] for the interrelated antioxidant roles of selenium and vitamin E:

where $a$ indicates possible damage to critical SH proteins, $b$ indicates possible lipid peroxidation and cell damage, $c$ indicates a possible blockage site for vitamin E, and $d$ indicates a possible catalytic protective effect on lipids by selenium as glutathione peroxidase (GSH-Px).

Isolation and identification of an enzyme with a specific or unique dependency on a trace element for normal metabolic function generally is considered a good indication of biological essentiality of the element. Metalloproteins have been identified, however, which may be mobilized in detoxification mechanisms, as has been suggested for the metallothionin response to cadmium challenge (94). An enzyme has been identified with a dependency on selenium for activity (118) and termed glutathione peroxidase (GSH-Px) since it has demonstrated in vitro protection of erythrocytes from oxidative damage produced by peroxides derived from unsaturated fatty acids within the cells (117). The isolated enzyme (GSH-Px) from bovine erythrocytes probably contained 4 g atoms of selenium per mole and no other metal and weighed 84,000 daltons. Each of four subunits contained 1 g atom of selenium (27). The GSH-Px from ovine erythrocytes was similar (62).

Very recent reports have shown that GSH-Px activities in tissues of rats (16, 61) and chicks (111, 125) were responsive and dose-related to dietary selenium. In male rats, GSH-Px enzyme activity was more sensitive to dietary selenium supplementation or deficiency in plasma, kidney, and heart than in erythrocytes, lung, liver, and testes (16). In chicks, no differences were found between GSH-Px activities when supplementary selenium was equiva-
enzyme systems such as xanthine oxidase, amino acid oxidases, etc.

oxidant stressors

unsaturated lipids → ROOH

ROH + H₂O

2GSH → GSSG

H₂O₂ → 2H₂O

H₂O + ½ O₂

catalase

[3]

lent as sodium selenite or selenomethionine (111). Cantor et al. (10), however, found selenite more effective than selenomethionine in producing the response in chicks. Dietary selenium, fed to newborn lambs for 8 wk with a low-selenium Torula yeast diet at increasing 0 to .5 ppm selenium, gave relatively increased tissue selenium in ten tissues studied with each addition of selenium (80, 108). Tissue GSH-Px activities, however, reached a plateau with .1 ppm supplementary selenium except in pancreas and erythrocytes. These authors have suggested that GSH-Px activity of tissue is extremely variable among species but may be a better indicator of dietary selenium adequacy in lambs than tissue selenium content.

According to Tappel (131), the GSH-Px system functions in the aqueous phase of cells and vitamin E is stored and functions in the lipid portions of the cell’s membrane parts. A strong case has been put forth in the literature for the antioxidative function of selenium. There are those, however, who question such a single role for selenium and continue to investigate other possible functions (61). It has been suggested (141) that the cupreins or superoxide dismutase were more active in aerobic conditions than GSH-Px in protection of mitochondrial membranes from the reactions of oxygen with such reducing systems as the unsaturated fatty acids, and that catalase is an efficient peroxide neutralizing agent. It is still not known whether the damaging “free radicals” in vivo may be peroxides, superoxides, or singlet oxygens. Clarification of the “antioxidant” role of selenium in relationship with other cellular oxidation-reduction systems is awaited with interest. Oregon investigators (7, 143) have studied seleno-proteins of ruminant serum, effects of selenium on protection of protein sulfhydryls, and possible relationships of selenium to cytochromes and oxygen metabolism. Several investigators have suggested an electron transfer role for selenium (20, 84, 85, 86) in cytochrome systems. It has not been possible always to duplicate or reconcile results in vitro with enzyme responses in vivo. The improved status of animals with selenium-responsive disorders to supplemental selenium remains essentially unexplained.

INTERRELATIONSHIPS

The complex nutritional interrelationships among selenium, vitamin E, lipids, sulfur, and the sulfur amino acids have challenged many investigators. Some of these interrelated effects on bioavailability and metabolism of selenium are presented briefly. Among species, the effects of varying these nutrients in the diets of animals with selenium/vitamin E-responsive disorders have not been uniform. Dietary alterations of any one nutrient may alter the dietary requirement for any of the others. Such possible interactions have been discussed by others (30, 66, 70, 75, 109, 121, 130, 131, 136).

In swine, with an increase in confinement feeding and a reduction in access to pasture, dietary vitamin E activity becomes reduced significantly and the available dietary selenium becomes more critical (136). The usual corn-soy diet for swine, in addition, is generally low in sulfur amino acids (137). With ruminants under farm conditions, supplemental selenium has been effective in preventing NMD in lambs and calves, but it was ineffective against dystro-
phy produced experimentally with vitamin E deficient diets supplemented with unsaturated fats (71). In the latter condition, supplemental vitamin E was required in addition to selenium for protection.

There have been few reports on the trace mineral status of any of the animals in which Torula yeast or soy diets have been used to study selenium/vitamin E responsive diseases. Growing lambs were fed purified Torula yeast diets containing stripped lard as either artificial milk or pellets (26). Supplementation with increased dietary vitamin E and 1 ppm dietary selenium significantly increased muscle and liver selenium concentrations. As dietary vitamin E increased without supplemental selenium, however, muscle and liver selenium declined progressively. In a subsequent experiment (25) with young swine receiving a Torula yeast diet, reductions in hemoglobin and in tissue copper and iron occurred as the experiment progressed but were not affected by selenium or vitamin E supplementation. Liver and kidney manganese, however, increased with selenium and/or vitamin E supplementation.

Canadian investigators have studied interrelated effects in the ruminant of selenium and/or vitamin E on NMD. Hidiroglou et al. (54) found that the presence or absence of 1 mg sodium selenite administered with 1 gm α-tocopherol per sheep weekly with a NMD-producing diet for 1 yr had no influence on the distribution of a tritium-labelled oral dose of α-tocopherol in blood and tissues of sheep. In lambs produced by ewes treated or untreated with α-tocopherol but without selenium, plasma tocopherol concentrations were not different. Direct administration of α-tocopherol to lambs provided protection from NMD mortality which occurred in untreated lambs, leading the authors to suggest that the vitamin E of milk was unavailable to lambs. Circulating tocopherol was reduced in pregnant but not in nonpregnant ewes when diets were supplemented with selenium without added vitamin E (6). Whether these results indicate that selenium is involved in the mobilization or utilization of vitamin E from ewe to milk or lamb tissues and could provide a sparing effect on available vitamin E for the animal is not yet substantiated.

Selenium may increase tissue turnover or mobilization of vitamin E in the rat (12, 13). In the chick, dietary selenium may be necessary to maintain production of pancreatic lipase and activity of trypsin for the hydrolysis and subsequent absorption of dietary lipids (134). Atrophy of the pancreas and failure of normal bile flow have been observed in selenium-deficient chicks. The relationship of rumen development in lambs to NMD and supplemental dietary vitamin E or ethoxyquin has been studied with Torula yeast diets containing .5 ppm selenium (18). Occurrence of NMD was not reduced following rumen development when animals consumed Torula yeast-lard basal diets. Polyunsaturated fat in muscle phospholipid and in adipose tissue was reduced generally by rumen development while vitamin E or ethoxyquin specifically reduced phospholipid linoleate concentrations and also occurrence of NMD. These authors recommended vitamin E supplementation of milk replacer diets which are high in polyunsaturated fatty acids. Phospholipid changes in liver and skeletal muscle of vitamin E-deficient versus vitamin E-supplemented calves also have been observed (24). Linoleate and arachidonate concentrations in muscle of dystrophic calves were increased compared to those of healthy calves in an earlier study (14).

Relationships of dietary selenium and linoleic acids on NMD development were studied in lambs and beef calves (71). Incidence of the disorder was reduced significantly when selenium was added to a diet of casein and low-selenium hay (20 ppb Se) without supplemental vitamin E for ewes (14 mg Se/wk) or lambs (7 mg Se/wk), but the disorder was not prevented completely. Supplemental dietary linoleic acid concentrate did not diminish selenium protection for the lambs when provided either to ewe or lamb. Selenium supplementation to diets containing added linoleic acid for calves completely prevented NMD but was not necessary for spontaneous recovery of afflicted calves. In the absence of added selenium, linoleic acid did not prohibit spontaneous recovery. The authors suggested that vitamin E of forage (15 ppm) in the diets was adequate and prevented a severe effect of dietary linoleic acid resulting in NMD. Fatty acids in forages consist largely of palmitoleic, linolenic, and linoleic acids. Only a small proportion of the total fatty acids in ruminant milk is saturated. Vitamin E content of cow's milk was 12 to 75 ppm of the lipid portion (87). A review of changes (49, 57) in milk fatty acids related to diet and NMD in calves born to
beef cows indicated inconsistent relationships and that a simultaneous evaluation of the selenium and vitamin E changes in milk should be undertaken. Viviani (139) suggested that a rapid increase of polyunsaturated fatty acids (PUFA) in tissues of young calves with a dietary vitamin E-selenium deficiency was significant to induction of NMD.

Hidiroglou et al. (55) suggested that cod liver oil is an antagonist to vitamin E in the ruminant. Among several possible explanations for the metabolic effect on tritium-labelled α-tocopherol uptake which were observed in cod liver oil-treated sheep versus controls, it was suggested that rumen bacterial growth may have been reduced by the PUFA's of the cod liver oil or that rumen bacteria may have synthesized α-tocopherol from phytol. Chow et al. (15) examined the effects in rats of dietary vitamin E on the activities of the GSH-Px system. Basal diets contained casein protein with either added cod liver oil or tocopherol-stripped corn oil. According to these authors, some of the changes in certain tissues reflected the higher peroxidizability of the PUFA's of the rats fed cod liver oil compared with those fed corn oil, but the muscle of rats fed cod liver oil was more resistant to tocopherol deficiency and muscular dystrophy than that of rats fed corn oil.

In a study of pastured cattle, Miltmore et al. (95) found no synergistic effect of selenium and/or vitamin E injections administered with injections of Ca-CuEDTA. The animals were considered to be consuming equal to or greater than adequate dietary selenium, and no toxicity was observed. The unthrifty animals were considered copper deficient or consuming inappropriate dietary ratios of copper to molybdenum.

Molybdenum is a trace metal involved in xanthine oxidase activity. This enzyme has been used to generate peroxides in in vitro experimental systems. Boyazoglu et al. (6) supplemented ovine diets with copper and molybdenum when studying effects of dietary sulfate on selenium utilization. Hematocrits were depressed in pregnant ewes with supplemental selenium, vitamin E, and high sulfate intake. Lambs were not protected completely from NMD by selenium supplementation, but incidence of the disorder with increased consumption of dietary sulfate was not as great as reported by others. Calves in a selenium-deficient area of northern Ontario were marginally copper deficient with a gradual plasma copper decrease (66 to 51 μg per 100 ml) over the first 20 wk of life (56). Copper and molybdenum status of the calves appeared unrelated to development of NMD.

It has been suggested by Gardiner (35) that cobalt deficiency in sheep reduced tolerance to high intakes of selenium. In addition, responses in gain to supplemental selenium were positive in New Zealand sheep when cobalt was given. Increased dietary protein also reduced the supplemental selenium requirement of sheep. It has been postulated that vitamin B₁₂ may be functional in methyl group metabolism and that detoxification of selenium may occur by methylation. Reduced vitamin B₁₂ due to cobalt deficiency might, therefore, inhibit the possible formation of trimethyl selenide ion or dimethyl selenide (19, 145). More recent Australian studies (81) are in progress with grazing sheep to study interrelationships of supplemental copper, cobalt, and selenium.

In rabbits, GSH-Px activity of red cells dropped to 26% of initial activity with the induction of nutritional iron deficiency (115). When rats were fed selenium-deficient diets with varying supplemental selenium (129), a relationship of the mixed-function oxidase enzyme systems in isolated liver microsomes to selenium status was observed, depending on the hormonal alteration of the rats. In swine, high dietary copper (>125 ppm) has altered the composition of adipose tissue with reduced proportions of saturated fatty acids (23, 132). Changes were identified as largely in the linoleic and palmitoleic fractions (3, 60), and the changes were influenced by dietary protein source (23). Vitamin E supplementation improved the oxidative stability of porcine depot fat (2). It appears that effects of dietary selenium and/or vitamin E may be related to the sulfur, copper, iron, and cobalt status of the animal as well as to dietary lipid and amino acid components.

Levander (83) reviewed certain metabolic interrelationships and adaptations of various species to selenium toxicity with such orally consumed substances as arsenic, linseed oil, methionine, and D-penicillamine. As a corollary to the known protective effects of selenium with certain heavy metal induced toxicoses (Ag, Hg, or Cd), Hill (59) and Jensen (74) have
demonstrated partial reversal of selenium toxicity in chicks by high dietary (500 ppm) cadmium, mercury, and particularly copper salts. The metabolic implications of dietary mineral imbalances for animals has been reviewed (8, 94).

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