

A brief history of selenium research: From alkali disease to prostate cancer (from poison to prevention)

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ABSTRACT: The trace element selenium has followed an unusual route on its way to becoming recognized as an essential nutrient. First feared as a plant toxin and later impugned as a suspected carcinogen, it has been shown to be required in the diets of animals and humans, in small quantities, and has been recognized as an effective anticarcinogen. Areas of selenium deficiency have been mapped, worldwide, and in them selenium supplementation has become an accepted practice. A number of means of administering selenium

have been developed, oral and by injection, and in the case of ruminant animals in heavy boluses, and it has been added to fertilizers to raise the selenium contents of forage and food crops. The supplementary uses of selenium with livestock have been shown to add only insignificant amounts of the element to the environment. Recent evidence shows that selenium may have generalized health-promoting abilities, operating through the immune systems, and its continued use in both animal and human populations seems assured.

Key Words: History, Nutrients, Selenium

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Introduction

When Berzelius discovered selenium in the sludge of sulfuric acid vats in 1817, he was looking for, and found, a toxic element that was contributing to worker illness in the acid plant. The Swedish manufacturers eliminated their plant health problem by changing the source of sulfur that they used, and very little was heard about selenium for over a century. It is doubtful that, brilliant as he undoubtedly was, Berzelius could have foreseen that selenium would eventually prove to be an essential nutrient and that it would stimulate so much scientific interest. Conor Reilly, who has chronicled the selenium scene for many years, estimated in 1996 that it had been the subject of over 100,000 technical papers (Reilly, 1996).

History

In 1937, A. L. Moxon published a report at the South Dakota Agricultural Experiment Station, in which he identified selenium as the toxic principle in some livestock-poisoning plants on the Western ranges (Moxon, 1937). The livestock problem, mistakenly called “alkali disease,” occurred in acute form following the consump-

tion by range animals of some wild vetches of the genus *Astragalus*, which accumulated toxic amounts of selenium from the soil (Beath et al., 1935). It could also occur, over time, from consumption of common forage crops grown in seleniferous areas. Affected animals lost much of the long hair in their manes and tails and suffered debilitating cracking and sloughing of hooves (Figure 1). And selenium was the culprit: certainly an inauspicious beginning for an essential nutrient!

In 1957, a German émigré biochemist, Klaus Schwarz, working at the National Institutes of Health in Bethesda, published a paper that changed forever the public conception of selenium (Schwarz and Foltz, 1957). Schwarz was concerned about problems of liver necrosis in laboratory rats he was feeding on a diet containing torula yeast as the source of protein. When he substituted baker's yeast (*Saccharomyces*) for the torula yeast, the problem disappeared, and after considerable study he was able to show that torula was deficient in selenium whereas *Saccharomyces* was not. He had thus identified the first “selenium-responsive” disease, and this led shortly to selenium being recognized as an essential trace mineral nutrient (McCoy and Westwig, 1969).

Schwarz's work stimulated a remarkable amount of research with selenium in large animal diets, much of which has been documented in the *Journal of Animal Science*, *Journal of Dairy Science*, and *Poultry Science*. Several metabolic diseases of previously unknown origin were found to relate to selenium deficiency, including “white muscle disease” in calves and lambs (Muth

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Figure 1. Alkali disease; severely damaged hoofs resulting from selenium excess.

et al., 1958), exudative diathesis in poultry (Patterson et al., 1957), hepatosis dietetica in pigs (Eggert et al., 1957), and pancreatic degeneration in poultry (Thompson and Scott, 1969). Although this useful field work was establishing the value of selenium in commercial animal production, some elegant studies at the University of Wisconsin showed that in producing its benefits, selenium was acting catalytically, as a part of the enzyme glutathione peroxidase (Rotruck et al., 1969).

Some problems remained, however. The U.S. Food and Drug Administration had to be convinced that selenium was safe at the recommended supplementary levels, and it cited studies suggesting that selenium was carcinogenic (Nelson et al., 1943). These studies involved rats that were fed diets inadequate in protein, to which selenium was added at levels much higher than needed to correct a selenium deficiency. The hypothesis was thus unsupported, and in 1973 scientists at the National Cancer Institute and the Food and Drug Administration issued a joint statement declaring that “judicious administration of selenium derivatives to domestic animals would not constitute a carcinogenic risk” (USFDA, 1973). More importantly, demographic surveys showed that, instead, selenium might be anticarcinogenic (Shamberger and Frost, 1969), and this has proven to be true. The issue of regulating selenium supplementation of feed animal diets has been reviewed by Ullrey (1992).

Areas of selenium deficiency have been mapped worldwide (Oldfield, 1999), and in them selenium supplementation is common. The well-known toxicity of selenium in excess has always engendered caution in its practical application, and fears of toxicity regained widespread interest when deaths and deformations of wild birds nesting at the Kesterson Reservoir in California’s San Joaquin valley were attributed to selenium

poisoning (Ohlendorf et al., 1990). Even though these excesses were traced to seleniferous shales bordering the valley and collected in runoff from agricultural irrigation, the situation raised questions anew about the safety of supplementation practices in animal agriculture. The Council for Agricultural Science and Technology assigned a task force to investigate this situation. Observed toxicities of selenium in nesting wild waterfowl at Kesterson were related to its bioaccumulation from agricultural drainage runoff, which contained high levels of selenium from natural soil sources. There was no reason to believe that the very low levels of selenium administered to livestock would significantly affect this situation. In fact, Ullrey (1992) calculated that the contribution of supplemental dietary selenium to total selenium in the environment would amount to less than 0.3%.

Selenium status can be measured with reference to various indicators. The soil is the ultimate source of selenium for plants, animals, and humans. Selenium concentrations tend to be lower in soils developed from igneous rocks than in those from sedimentary rocks and are generally lower in high-rainfall areas than in arid ones (Kubota et al., 1967). The total selenium content of soil, however, does not accurately present its availability in the food chain, and it needs to be considered in the light of other modifying factors, including redox potential and pH (Elrashidi et al., 1989). The selenium content of plants is a useful indicator of animal/human selenium status when plants are major components of the diet. From the Morrow plots at the University of Illinois, which have been continuously cropped since 1876, there is evidence that crop selenium concentrations are decreasing over time (CAST, 1994). The best criterion of selenium status in animals and humans is circulating blood concentrations, and there



Figure 2. Various boluses developed for administering selenium to ruminants, from the left: the original iron/selenium pellet, steel “grinder” to eliminate organic coating, and soluble glass boluses for sheep and cattle.

have been some differences of opinion about the most satisfactory measurement: whether it should be taken in plasma or whole blood and whether it might involve the selenoenzyme, glutathione peroxidase. There has been considerable acceptance of whole blood selenium as an indicator of medium- to long-term selenium status (Maas et al., 1993), although it has been noted that “there is no single test for selenium adequacy which can be considered superior in all diagnostic situations” (Wichtel, 1998).

In the course of many years’ experience in its nutrient use, a number of effective ways of administering selenium have been developed, including oral, parenteral, and fertilizer amendment technologies (Oldfield, 1997). These include the ingenious rumen boluses first developed in Australia (Kuchel and Buckley, 1969) and further developed elsewhere (Figure 2).

The focus of this work had been selenium supplementation of livestock, and it had been tacitly accepted that selenium supplementation of human diets that are drawn from numerous, diverse sources would probably be unnecessary. In New Zealand, where the livestock industry is a major contributor to the national economy, governmental agencies supported the addition of selenium to pasture fertilizers, and about 1.5 million hectares are now so treated (M. Shirer. Selenium fertilization in New Zealand. Ag. BioResearch; N.Z. Richmond, personal communication).

Meanwhile, however, evidence was accumulating that selenium supplementation of human diets might indeed prove beneficial at levels somewhat higher than usually considered nutritionally necessary. The impe-

tus for such investigations came first from China, where selenium-responsive diseases (Keshan disease and Kaschin-Beck disease) had already been demonstrated (Yang et al., 1988), but it soon spread to include other diseases and other land areas. It has now been suggested that selenium supplementation may be protective, to some extent, against certain types of cancer (Combs, 1997), cardiovascular disease (Duthie et al., 1989), and AIDS (Schrauzer, 1994). The most impressive evidence to date has come from a large-scale trial in which selenium supplementation brought about significant reductions in the incidence of cancer in the lung, colorectum, and prostate (Clark et al., 1996). In Finland, concern about selenium deficiency and human health was sufficiently strong that the government mandated selenium fertilization of croplands (Koivisto and Huttunen, 1986).

Another exciting development in our knowledge of selenium came with the demonstration that it could be protective against viral attacks (Levander, 2000). Working with coxsackie virus, these investigators found that a normally benign virus became pathogenic if exposed to selenium deficiency. Thus, in addition to its accepted roles in nutrition and metabolic disease, selenium could exert a protective action against viral infection.

It is interesting to reflect on this remarkable change in public awareness of the trace element selenium. Re-viled in the early 20th century as a poisoner of livestock—where as many as 60% of an exposed animal population would show symptoms of alkali disease and some would die—selenium closed the millennium with

the demonstration by Clark and colleagues at the Arizona Cancer Center of the promise of protecting a similar percentage of humans (>60%) from the ravages of prostate cancer (Clark et al., 1996). It is also thought-provoking that much of our current encyclopedic knowledge of selenium was gained through experimentation with domestic animals, and a good deal of this was documented in the *Journal of Animal Science*. This metamorphosis is apparent in recognized textbooks of the era. The last (22nd) edition of Morrison's *Feeds and Feeding* (1957) recounted two paragraphs on selenium poisoning—nothing on its nutrient qualities, whereas Ensminger's *Feeds and Nutrition*, which supplanted *Feeds and Feeding*, devoted six paragraphs to selenium's beneficial effects and one to its toxicity (Ensminger et al., 1990). Surely, few substances have enjoyed such a dramatic, conceptual turn-around since their original discovery.

Implications

Benefits from selenium supplementation in areas of soil deficiency have been shown to be both effective and safe. Mapping areas of deficiency worldwide has aided in defining areas where selenium administration may be useful. Selenium may be given directly to animals or humans, orally or by injection, and it may be added to fertilizers to enhance the selenium contents of forages and food crops.

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