Selenophilia

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'Selenophilia' is the name that has been given to the current strong interest in the use of selenium, over and above normal and apparently adequate levels of dietary intake, for the prevention, alleviation or cure of a variety of disorders which have not been shown to be directly associated with Se nutrition. The term includes the interest and use of Se supplements by both the general public and medical–nutritional professionals. Excluded, however, are the conditions which have been shown to be directly (if not always entirely) related to a very inadequate intake of Se and which can be prevented or cured by giving additional Se alone. In this category is the disorder found mainly in China: Keshan disease, the principal feature of which is cardiomyopathy, and the skeletal myopathy that has been recorded in patients on total parenteral nutrition with insufficient Se in the infusate (Levander, 1985).

Se as an essential nutrient

Investigations of the biological role of Se were initially concerned with its toxicity. Se poisoning was identified in 1934 as the cause of lameness and death in livestock grazing areas of the Dakotas and Wyoming where it was discovered that some soils and plants had exceptionally high levels of available Se (National Research Council, 1983). Recognition of the element as an essential nutrient may be dated from the work of Schwarz & Foltz (1957), when they showed that Se was the active principle in yeasts which could prevent the liver necrosis caused by deficiency of vitamin E in the rat. Subsequently a number of economically important disorders in farm animals were shown to be caused by Se deficiency, including nutritional myopathies in numerous species and unthriftiness in cattle and sheep. Extensive areas have been identified around the world where the Se in the soil is very low or unavailable, and feeds and crops for both animal and human consumption grown on these soils contain low levels (less than 0·1 mg/kg) of Se (National Research Council, 1983).

Interest in the role of Se in human nutrition was well developed by the mid-1960s (Burk *et al.* 1967), and it is not surprising that it has since been largely centred on the possible involvement of Se in human disorders which have features similar to those of the Se-responsive disorders in animals. The discovery in 1973 that glutathione peroxidase (*EC* 1.11.1.9; GSHPx) is a selenoenzyme, and is the major active form of Se in the tissues, provided in large measure a biochemical explanation for the observed pathological changes in deficiencies (Flohé *et al.* 1973; Rotruck *et al.* 1973). This discovery stimulated a further flurry of interest in Se by nutrition researchers, which has more recently been expanded to a broader medical and, indeed, lay 'audience' by the current focus on the possible causative role in human diseases of in vivo-generated free radicals and oxygen intermediates.

GSHPx contains 4 gram-atoms Se/mol, which is present at the active sites as selenocysteine. The enzyme, acting in concert with other antioxidants and free-radical scavengers in the cell, reduces hydrogen peroxide and organic peroxides to water and corresponding alcohols, in the presence of reduced glutathione (National Research Council, 1983). Fig. 1 outlines the activities and relations among GSHPx, vitamin E, superoxide dismutase (*EC* 1.15.1.1) and catalase (*EC* 1.11.1.6) in cellular protection.

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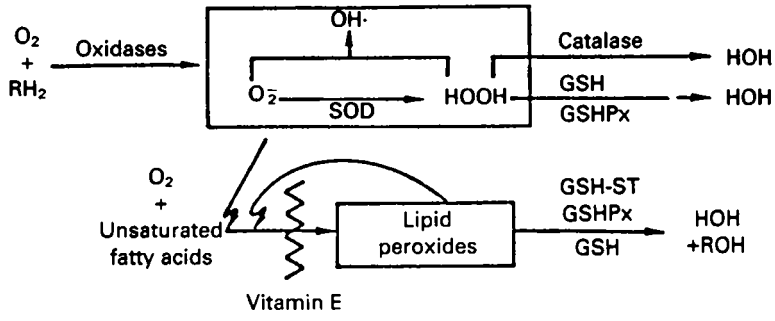

Fig. 1. Interrelations among cellular antioxidants. Catalase, (*EC* 1.1.11.6) glutathione peroxidase (*EC* 1.11.1.9; GSHPx) and superoxide dismutase (*EC* 1.15.1.1; SOD) catalyse the reduction of the highly reactive forms of oxygen produced during oxidative metabolism. Vitamin E scavenges free radicals produced by the reaction of O_2 with unsaturated fatty acids in membranes. GSH, glutathione; GSH-ST, glutathione-S transferases. (Adapted from National Research Council, 1983.)

Whereas vitamin E is present in cell membranes, GSHPx acts in the cytosol and mitochondrial matrix. In some animal models, one nutrient may protect, to a certain extent, against the deleterious effects of the other, but this does not appear to occur in humans. (The activity of catalase is complementary to that of GSHPx in that it degrades H_2O_2 only and acts in the peroxisome.) The proportion of total Se which is present in GSHPx and the relative amount of GSHPx vary among tissues in one species and, for a given tissue, between species, an important consideration in extrapolation of animal studies on Se to human situations (Ganther *et al.* 1976).

Se nutrition in different populations

Se, like iodine and fluorine, is metabolized in anionic form. For such elements, tissue levels are much more readily influenced by dietary intakes than is the case for metallic elements like zinc, for which absorption is the major homeostatic mechanism (Mertz, 1985). Nutritional status with respect to Se, therefore, to some extent reflects the level of availability of Se in the geochemical environment. Outside areas of frank deficiency or toxicity, human dietary intakes of Se are usually in the range 30–300 μg/d. (The (US) National Research Council (1980) has established an estimated safe and adequate daily intake of Se of 50–250 μg/d.) In general, the average blood level of Se in the healthy adult population reflects the average dietary intake of the group (Nève *et al.* 1985), and the status of human populations in different regions tends to follow the pattern of Se status in livestock around the world, as shown in Fig. 2.

A useful division of human groups may be made according to blood levels of Se: (1) overt clinical deficiency is associated with blood levels <10–15 ng/ml; (2) areas where animals require Se supplementation but no recognized human problems (blood levels 40–75 ng/ml, intakes 20–50 μg/d), regarded as low-Se areas; (3) no livestock problems (blood levels 80–250 ng/ml), Se-adequate areas; (4) areas where toxicity occurs in animals (blood levels >300 ng/ml), high-Se areas.

Selenophilia

Belief in the desirability or usefulness of Se supplementation is by no means confined to countries or areas where dietary intakes are low.

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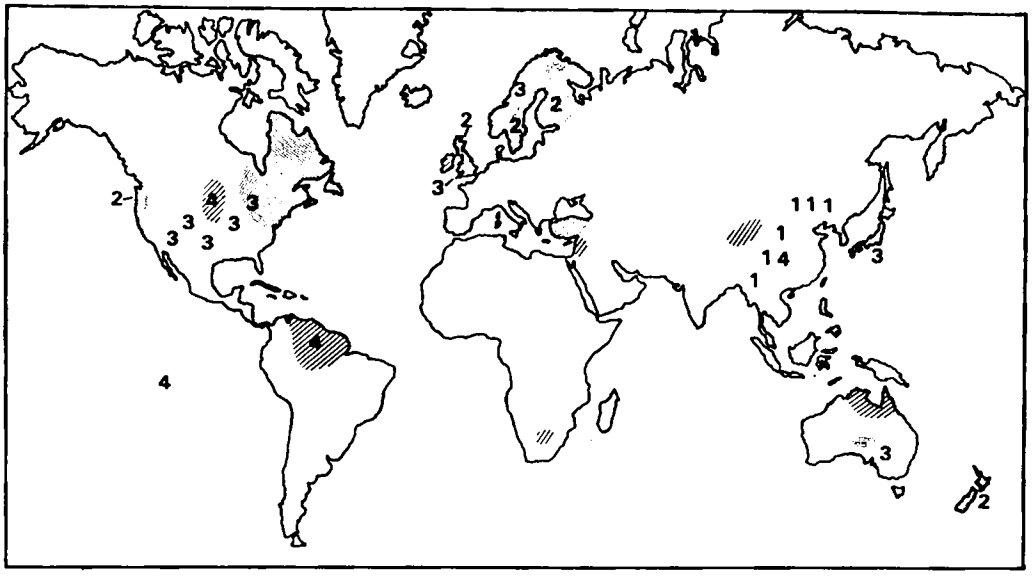

Fig. 2. Average blood levels of selenium in the human population of various regions, in relation to areas where Se deficiency (▨) and toxicity (▩) occur in livestock. Human blood levels (ng Se/ml): 1, <30; 2, 40–80; 3, 80–250; 4, >300.

In the United States, where the taking of dietary supplements is common, one may choose from more than sixteen different preparations which provide Se alone as an inorganic salt or 'yeast', in combination with vitamin E, or in a 'top-of-the-line' antioxidant mixture which contains Se, vitamins E and C and superoxide dismutase. Fewer Se preparations are sold in the UK; I found only three. Including those available in both countries, suggested daily doses give between 10 and 250 μg Se costing from 2–36 cents (1·5–24 p) for 100 μg, compared with a cost of 0·008 cents for 100 μg Se from laboratory-grade sodium selenate. These observations were made in a Se-adequate area (London) and a high-Se area (Colorado). Of the two Western countries with the lowest natural levels of Se, New Zealand does not allow sales of supplemental Se for human consumption; for Finland, I was not able to obtain values on supplement usage but quote from a recent paper discussing the Government mandated scheme for raising the level of Se in the national food supply: '. . . do-it-yourself and prescribed selenium supplementation has become popular and the . . . pill business has boomed' (Koivistoinen & Huttunen, 1985). Table 1 lists some of the conditions for which the beneficial effects of Se supplementation are urged by suppliers.

Table 1. *Disorders and conditions for which selenium supplementation has been advocated by supplement suppliers and popular writers*

Ageing	Cystic fibrosis	Radiation protection
Arthritis	Cardiovascular disease	Increasing birth rate
Cancer	Muscular dystrophy	Combats oxidative and pollutant damage
Cataracts	Sudden infant death syndrome	'Somewhat mysterious' uses in the body

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Within the health professions, interest in the role of Se in human health and disease is, if anything, even stronger. As an indication, *Index Medicus* lists a total of 4618 papers concerning Se published between 1966 and 1985, an average of 230/year. Over 500 of these were concerned with one area of major and increasing interest: the possible role of Se in the prevention of human cancers. In spite of all this work, however, there are still many unanswered questions concerning Se nutrition in humans.

Effects of Se supplements

A problem with many trace elements, including Se, is establishing criteria by which to judge the adequacy of a level of intake. The daily intake required to maintain Se balance appears to vary according to the customary level of intake: in low-Se areas of China, balance was achieved at an intake of 20 μg/d (Yang *et al.* 1984), compared with 24 μg/d for New Zealand women (Stewart *et al.* 1978) and 54 μg/d for North American men (Levander *et al.* 1981). This poses the question of whether maintaining balance, without frank deficiency, does in fact reflect adequacy of intake, or whether extra benefit to health may be conferred by higher intakes with consequent higher levels of Se in the tissues.

The answer may, in part, be provided by some functional aspect of Se, i.e. GSHPx activity. In humans, only that in the blood can be measured routinely and it is not known how this relates to activity in other tissues. In populations in which most individuals have blood Se levels greater than 100 ng/ml, no relation is seen between Se and GSHPx activity. However, in a very large study which included Se-deficient patients, healthy New Zealanders and visitors from other countries, Robinson's group (Rea *et al.* 1979) in Dunedin were able to examine individuals with a very wide range of blood Se levels: from 15 to 450 ng/ml. They found a strong, direct relation between whole-blood GSHPx and Se levels in plasma or erythrocytes, up to a Se level of 140 ng/ml, with a plateau in enzyme activity above this concentration (Rea *et al.* 1979). It has been suggested that the plateauing of GSHPx activity may indicate that the Se requirement for the enzyme had been met, and that a dietary intake sufficient to maintain this enzyme level represents the dietary requirement (Robinson & Thomson, 1981).

Both Robinson's group in New Zealand and Levander and co-workers in Finland (Levander *et al.* 1983; Thomson *et al.* 1985) have conducted extensive studies on the effects of various sources of supplemental Se on the concentrations of Se and GSHPx activity of different blood fractions. In general all Se sources (including selenite, selenate, Se-rich wheat, Se-rich yeast and Se-rich fish) caused increases in Se levels in whole blood, plasma and erythrocytes in subjects whose initial Se status was relatively low. The extent and duration of increases varied according to Se source. GSHPx activity also increased, particularly in platelets, but the extent of the increase was usually less than that of Se and tended to show the same plateauing that was observed in the cross-sectional study (Levander *et al.* 1983; Thomson *et al.* 1985).

In spite of the fact that Se and GSHPx levels in blood can be raised by supplementation in individuals living in low-Se areas, in the absence of clinical deficiency, there is no good evidence that the health of such populations is any way compromised by their lower Se status. There is even less evidence to suggest that a Se intake greater than that which will maximize blood GSHPx activities is beneficial. Nonetheless, there continues to be a pervasive feeling that people in low-Se areas should be less healthy, or more susceptible to diseases for which Se is reputed to have a protective role, compared with their fellows in better-endowed regions. The most prominent of such disorders, for which a beneficial effect of a higher intake of Se is claimed, is cancer.

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Se and cancer

Cancers cause about 25% of all deaths in the 35–64 years age-group in most Western countries. A definite causative agent can be assigned to no more than about 10% of all cancers (Doll & Peto, 1981) and, in the search for factors in the environment that increase susceptibility to or protect against the development of cancer, Se is currently attracting a lot of attention.

A large number of studies have shown that Se has a marked influence on the development of tumours in several species of experimental animals. The majority of such studies have investigated chemically induced tumours in liver, colon, mammary or epidermal tissue of rats or mice. Results vary according to experimental conditions and not all workers have obtained positive results, but, in general, an adequate intake of Se compared with a deficiency, or Se added to an adequate diet, reduced the incidence or increased the induction time of tumours by up to 90% of control values. The effects of Se vary with the form and regimen of administration and may be modified by other dietary factors such as vitamins A and E (Griffin, 1979; Carroll, 1985). Se appears to act at the promotional stage of carcinogenesis but the actual mechanism is unknown.

As well as the usual precautions necessary when extrapolating cancer studies in animal models to the human situation, several other points must be considered with respect to Se. The disposition of Se (e.g. the proportion present a GSHPx) varies from tissue to tissue within a species and between species for the same tissue. There is evidence that the antitumorigenic action of Se is not mediated through its antioxidant activity, but possibly through a more direct interaction of Se with metabolites of tumour-inducing chemicals (Poirier & Milner, 1983; Ip, 1985). Highly positive results may, therefore, be expected in animal studies in which tumours are induced by a single chemical. Less than 1% of human cancers, however, can be attributed to direct action of a carcinogenic chemical (Doll & Peto, 1981). A protective effect exerted by direct chemical interaction would be enhanced by the subtoxic levels of Se supplementation used in many animal studies. Given the potential for toxicity of many Se compounds, supplementation of human intakes to comparably high levels is not practicable, and indeed as yet, there is no evidence to suggest it may be desirable.

The evidence that Se, within the ranges of intakes that occur naturally, protects against cancer in human populations is, at best, equivocal. There are several studies which appear to show a relation between Se in the blood and cancer incidence, internationally and within the USA: Schrauzer *et al.* (1977) showed a significant correlation between total cancer mortality in twenty-seven countries with Se intake, calculated from food disappearance values and an average value for the Se concentration in the main food items. However, it is now known that Se content varies very widely with the area of production, especially for staple cereal crops. Shamberger & Willis (1971) and Shamberger (1985) compared age-specific death rates of cancer with average levels of Se in blood from healthy donors, from the fifty states of the USA. Average cancer mortality was highest in the states in the lowest quintile of Se values, but the difference was only 1·3-fold. The range of cancer rates in individual states was within the range for those states in the highest third.

Taken together, these and other studies by the same workers, suggest that if Se has an effect on the population rates of human cancer mortality, it is not strong. We did a similar exercise, of comparing rates of different cancers with Se status in a number of countries, with negative results. Fig. 3 shows such comparisons for breast and colorectal cancers in eleven developed countries. Plasma Se concentrations are published values for healthy adults in New Zealand (Robinson & Thomson, 1981); Finland (Levander *et al.*

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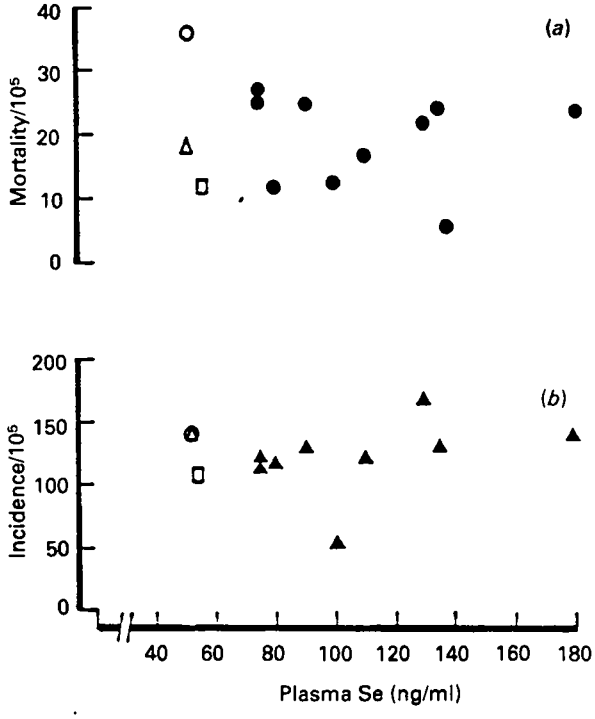

Fig. 3. Occurrence of cancer in (*a*) twelve and (*b*) eleven countries in relation to plasma selenium levels in healthy adults in the same areas. (*a*) Age-adjusted mortality rates for colorectal cancer in males, 35–64 years. (*b*) Age-adjusted incidence rates for breast cancer in females. ○, New Zealand, non-Maori; △, New Zealand, Maori; □, Finland; ● and ▲, other countries. (Information from International Agency for Research on Cancer (1982).)

1983); Scotland, Australia, Denmark, Norway and England (Iyengar, 1985); Japan (Hatano *et al.* 1984); and Sweden, Canada and the USA (Nève *et al.* 1985). The rates for total incidence, and incidences of breast, liver, prostate and lung cancers, were taken from International Agency for Research on Cancer (1982), and mortality rates for colorectal cancer from Smith *et al.* (1985). All cancer rates are age-adjusted for 35–64 years, and, where available, are for the same area within a country as the Se analyses. Values from New Zealand are reported separately for Maoris and Pakehas (non-Maoris, 98% of European extraction), to show the very wide differences in colorectal rates in two groups with similar low Se exposure and with similar diets. As can be seen from Fig. 3, there was no obvious relation between cancer rates and blood levels of Se for breast or colorectal cancer; nor was any relation seen for Se and incidence for all sites, liver, prostate or lung cancers.

A slightly better case for a role of Se in cancer chemoprevention can be made from the results of several recent studies in which Se levels in blood collected prospectively were compared at a later date for individuals who developed cancer with levels in those who did not. Table 2 summarizes results from two reports, one from the USA (Willett *et al.* 1983) and one from Finland (Salonen *et al.* 1985). In both, a significantly greater than expected cancer mortality was found in individuals in lower blood Se groups: for the USA study, the lowest tertile, <115 ng/ml, for the Finnish study, <47 ng/ml. In the American group, the increased risk from highest Se to lowest was 2·4, compared with 5·8

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Table 2. *Selenium and cancer: prospective studies*

	USA (Willett *et al.* 1983)		Finland (Salonen *et al.* 1985)	
Plasma Se (ng/ml)	>154	<115	>47	<47
Relative risk of cancer	1	2·4	1	5·8
Total cancer (/10^5)	406		362	

in Finland. In both studies, the strength of the association was increased when blood levels of vitamins A or E were included in the statistical analysis.

Although these studies suggest that higher Se status is related to a lower incidence of cancer, several issues need to be addressed. (1) The numbers of subjects in both studies were small, particularly when confounding variables were included in the analysis. The ability to separate cancers at different sites may strengthen the relation. (2) The highest levels of Se in the Finnish subjects were lower than the lowest in the American cases. (3) Total cancer incidence in Finland is lower than that in the USA, as are rates of several of the cancers most associated with Se chemoprevention studies in animals (breast and colorectal).

If the relation found in these studies holds with larger numbers, in different countries, and with site-specific cancer rates, they suggest that different intakes of Se provide the same level of protection in different populations, perhaps because of different levels of exposure to causative agents.

Conclusions

Se-responsive disorders are widespread in animals. However, there is little evidence for similar problems in man, with the exception of areas of endemic Keshan disease. Although there are currently many proponents for Se supplementation, either of the individual or on a population basis, on balance, there is little evidence at present that such will be of any practical benefit, either with respect to cancer prevention, or in promoting a more general improvement in health and well-being. Self-medication with Se cannot be regarded as harmless; Se has a narrower range of safety than many other trace elements and there have been a number of cases of toxicity reported in the USA in individuals who were taking high levels of supplemental Se (Levander, 1985).

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