

The Importance of Selenium to Human Health

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The trace mineral, selenium (Se), is an essential nutrient of fundamental importance to human biology. This has become increasingly obvious in recent years as new research has revealed a hitherto unsuspected role for this element in areas of vital importance to human health.

As selenocysteine, the 21st amino acid, it is a component of selenoproteins, some of which perform important enzymic functions (see Table 1).¹ Only recently has it been recognised that all these enzymes are Se-dependent, generally with selenocysteine at the active site.¹ Here Se functions as a redox centre, for instance when the selenoenzyme, thioredoxin reductase reduces nucleotides in DNA synthesis and helps control the intracellular redox state,² or when the selenium-dependent iodothyronine deiodinases produce active thyroid hormone from inactive precursor.¹ The best-known example of this redox function is the reduction of hydrogen peroxide and damaging lipid and phospholipid hydroperoxides to harmless products (water and alcohols) by the family of selenium-dependent glutathione peroxidases.^{1,2,3} This helps to maintain membrane integrity,^{3,4} protects prostacyclin production⁴ and reduces the likelihood of propagation of further oxidative damage to biomolecules such as lipids, lipoproteins and DNA with the associated increased risk of conditions such as atherosclerosis and cancer.^{3,4} Around 35 selenoproteins have been identified, though many have roles which have not yet been fully elucidated.⁵

Se has additional important health effects, particularly in relation to the immune response and cancer prevention, which are almost certainly not exclusively linked to these enzymic functions.

Health conditions with a recognised selenium-deficiency aetiology

Recognition of the important role of selenoproteins in metabolism helps to explain the adverse consequences of Se deficiency in human and animal health. Se enters the food chain through plants which take it up from the soil. Se deficiency has therefore been identified in parts of the world, such as volcanic regions, notable for their low soil Se.¹⁰ Acid soils and complexation, frequently with iron or aluminium, also reduce the uptake of Se by the plant, as in many parts of Europe.¹⁰ Animal deficiency diseases have been identified since the 1950s on a wide scale in livestock in a number of countries, including the UK, that have such soil conditions, examples being reproductive impairment, growth depression (Ill-thrift) and White Muscle Disease, a myopathy of heart and skeletal muscle, principally affecting lambs and calves.¹⁰ These conditions have had such serious economic consequences that measures to increase Se intake (e.g. top dressing of pasture land with selenised fertilizers, mineral mixes, boluses, drenches) are now applied to prevent their occurrence.¹⁰

Human dietary intakes also range from high to low according to geography. Human Se-deficiency diseases have been recognised in some regions: Keshan Disease, an endemic cardiomyopathy, and Kashin-Beck Disease, a deforming arthritis were first identified in an area of China where the soil is extremely low in selenium.¹⁰

Health effects of less-overt selenium deficiency

There is evidence that less-overt Se deficiency can have adverse consequences for disease susceptibility and the maintenance of optimal health. Low Se status may contribute to the aetiology of the disease process but it is also necessary to be aware that in some cases, lower Se status may be an outcome of the condition itself and may exacerbate disease progression (e.g. HIV infection, see below). These difficulties are largely overcome in

prospective epidemiological studies, particularly where the first few years of follow-up are excluded from the analysis, and in prospective, randomised, controlled clinical trials of Se supplementation.

Immune function

Numerous studies suggest that deficiency of Se is accompanied by a loss of immunocompetence, probably not unconnected with the fact that Se is normally found in significant amounts in human immune tissues such as liver, spleen and lymph nodes. Both cell-mediated immunity and B-cell function can be impaired.⁶

In contrast, supplementation with selenium, even in “selenium-replete” individuals, has been shown to have marked immunostimulant effects, including an enhancement of proliferation of activated T-cells otherwise known as clonal expansion.¹¹ Lymphocytes from subjects supplemented with selenium (as sodium selenite) at 200 mcg/day, showed an enhanced response to antigen stimulation and an increased ability to develop into cytotoxic lymphocytes and destroy tumour cells. Natural-killer(NK)-cell activity was also increased. The supplementation regime resulted in 118% increase in cytotoxic-lymphocyte-mediated tumour cytotoxicity and an 82% increase in NK-cell activity as compared to baseline values.¹¹

The mechanism appears to be closely related to the ability of Se to upregulate the expression of receptors for the growth regulatory cytokine, interleukin-2 (IL-2) on the surface of activated lymphocytes and NK cells, thereby facilitating their interaction with IL-2. This interaction is crucial for clonal expansion and differentiation into cytotoxic T-cells. Results of this study indicate that even at so-called replete levels of plasma Se produced by normal dietary intake in the US, i.e. 120-134 mcg/L, supplementation with 200 mcg Se has considerable immunoenhancing effects.¹¹

Additionally, cells of the immune system may have an important functional need for Se. Activated T-cells show upregulated selenophosphate synthetase (SPS2) activity,¹² directed towards the synthesis of selenocysteine, the essential building block of selenoproteins, demonstrating the importance of selenoproteins to activated T-cell function and the control of the immune response. The mRNAs of several T-cell associated genes (e.g. IL-2 receptor α -subunit, CD4, CD8) have the theoretical capacity to encode functional selenoproteins, suggesting that the roles of Se in the immune system may be more diverse than previously suspected.¹³

Viral infection

Se deficiency is linked to incidence, virulence or disease progression of a number of viral infections.¹⁴

Elegant work by Beck and colleagues has shown that in a selenium-deficient host, harmless viruses can become virulent,¹⁵ a situation which is likely to be relevant to the development of the endemic human selenium-deficiency cardiomyopathy, Keshan Disease. When Se-deficient mice were inoculated with a benign strain of the coxsackie virus (CVB3/0), mutations occurred in the genome to give a cardiovirulent form of the virus which caused myocarditis with similarities to human pathology. Furthermore, when the virus recovered from these mice was inoculated into *Se-adequate* mice, it still induced significant heart damage, demonstrating the irreversibility of the mutation. In the case of the coxsackie virus, six separate point mutations were identified with the development of virulence, causing myocarditis in the host. A similar study on mice unable to make GPx1 (GPx1-knock-out mice) demonstrated that this enzyme is essential for the avoidance of oxidative damage to the RNA-viral genome which results in the myocarditic mutations.¹⁵

Coxsackie virus has been isolated from the blood and tissues of Keshan Disease

victims and is thought likely to be a co-factor in the development of the cardiomyopathy which constitutes this condition.¹⁵ It seems probable, therefore, that human Se deficiency similarly affects the viral genome resulting in the development of the heart pathology.

If these findings were to be applicable to other RNA viruses, e.g. polio, hepatitis, influenza or HIV, there would be considerable public-health implications. The steady emergence of new strains of influenza virus in China with its selenium-deficient belt, or the first crossing over of HIV to humans in the selenium-deficient population of Zaire, might also be explained.¹⁵

Se seems to be a crucial nutrient for HIV infected subjects. It is a potent inhibitor of HIV replication *in vitro*.¹⁶ The progress of HIV can be thought of as being synonymous with the progressive loss of CD4+ helper T-cells. More than 20 papers report a progressive decline in plasma Se paralleling the on-going loss of CD4+ T cells in HIV-1.¹⁷ This occurs even in early stages of disease where malnutrition or malabsorption cannot be a factor.¹⁷ In fact, plasma selenium is a strong predictor of the outcome in HIV infection. Work carried out by Baum and co-workers at the University of Miami showed that selenium-deficient HIV patients are 19.9 times more likely (95% CI 5.52-71.9; $p < 0.0001$) to die from HIV-related causes than those with adequate levels.¹⁸ Selenium deficiency is defined by Baum as a plasma level at or below 85 mcg/L, a level not attained in many northern European countries (see below), e.g. a mean level of 60 mcg/L was found in a recent Scottish study.¹⁹ Baum showed that low plasma Se is a significantly greater risk factor for mortality than low helper T-cell count, by a factor of 16, and confers a much more significant risk than deficiency of any other nutrient investigated. In HIV-infected children, low levels of plasma Se were significantly and independently related to mortality (RR 5.96, 95%CI 1.32-26.81; $P = 0.02$) and faster disease progression.²⁰

Se also appears to be protective in subjects infected with hepatitis-virus (B or C) against the progression of the condition to liver cancer (see section on Cancer).^{21,22}

It is notable that viruses may be capable of hijacking the Se supply of the host by incorporating Se into viral selenoproteins thereby reducing the ability of the host to mount an effective immune response. There is experimental evidence that this is possible from the work of Moss's group in the case of the pox virus, molluscum contagiosum, which makes a homologue of GPx²³ and both theoretical and experimental evidence from Taylor's group that the capability of making viral selenoproteins (such as GPx) is common to many human viral pathogens such as HIV-1 and 2, coxsackie virus B3, hepatitis B and C, and the measles virus.²⁴ Good Se status may protect against HIV progression by maintaining host immune competence and appropriate redox control. Taylor suggests that as long as there is enough Se around, cellular immunity will be high and the host cell will be less likely to die (by apoptosis). The best viral strategy is therefore to replicate at very low levels and establish a persistent infection. Under low Se conditions, however, increased oxidative stress and apoptosis activate the virus, which must replicate at higher rates to escape from a dying cell thus leading to increased pathogenic effects.

Reproduction

Selenium has long been recognised in animal husbandry as being essential for successful reproduction.²⁵ Idiopathic miscarriage has been shown to be associated with Se deficiency in veterinary practice²⁶ while in sheep, administration of Se supplements has been shown to prevent early pregnancy loss.²⁷ Investigating whether this could also be relevant to humans, Barrington found significantly lower serum Se in women who suffered either first-trimester or recurrent miscarriages.^{28,29} He suggests that early pregnancy loss may be linked to reduced antioxidant protection of biological membranes and DNA by relatively low levels of the Se-dependent GPx. A subsequent study found lower Se levels in non-pregnant women

suffering recurrent miscarriage than in controls, but the difference did not reach significance.³⁰ However, the choice of control group can be criticised in this study as it did not exclude women who had suffered a miscarriage.

Se is essential for male fertility, being required for testosterone biosynthesis and the formation and normal development of spermatozoa.³¹ Se concentration of seminal plasma correlated positively with concentration of spermatozoa in a group of sub-fertile Norwegian men.³² Animals fed Se-deficient diets show structural abnormalities in the sperm midpiece which are linked to poor motility and a tendency for the tail to break off³³ thus decreasing the chance of fertilisation. An explanation for these findings has recently been afforded by the work of Ursini and colleagues.⁷ They found that a form of glutathione peroxidase (GPx4), believed to shield developing sperm cells from oxidative damage, polymerises in mature sperm into a structural protein in the mitochondrial capsule of the midpiece region. As GPx4 accounts for about 50% of the capsule material, it seems likely that it is this polymerisation that confers the structural integrity required for sperm stability and motility.

Work carried out at Glasgow Royal Infirmary supports this interpretation.³⁴ In studies by Scott and co-workers, supplementation of subfertile men with 100 mcg selenium per day for three months significantly increased sperm motility. Eleven percent of men receiving the active supplement achieved paternity as compared with none in the placebo group. However administration of double the quantity of selenium to subfertile Polish men over a similar period, showed no beneficial effect on sperm motility.³⁵

Mood

There are a number of indications that Se is important to the brain:- during Se depletion the brain receives a priority supply;³⁶ the turnover rate of some neurotransmitters is altered in Se deficiency;³⁷ supplementation with Se reduced intractable epileptic seizures in children;^{38,39} low plasma Se levels in the elderly were found to be significantly associated with senility and accelerated cognitive decline;^{36,40} brain Se concentration in Alzheimer's patients was only 60% of that in controls.³⁶ Furthermore, the brain is deficient in catalase,³⁹ thus peroxidation products such as H₂O₂ and primary peroxides must be removed by the antioxidant selenoenzymes.

A number of studies have shown a beneficial effect of Se status on mood at least when Se-status is "marginal". In three separate studies, low selenium status was associated with significantly greater incidence of depression and other negative mood states such as anxiety, confusion and hostility.^{36,41,42} Mood was measured by use of a questionnaire, the "Profile Of Mood States - Bipolar form (POMS-BI)". The higher the score, the better the mood.

In a study carried out in the US, Se deprivation led to depressed mood and more hostile behaviour.³⁶ The lower the initial Se status, the more the mood scores decreased as a result of the low Se diet. In a second US study, where subjects were fed either a low or a high Se diet for 15 weeks, those on the low Se diet had significantly decreased clearheaded/confused and elated/depressed subscores.⁴¹ (The dietary Se intake on this low-Se diet was 32.6 mcg/d, similar to current UK intakes of 29-39 mcg/d.⁴³)

In contrast to these findings, high dietary Se or supplementation with Se appears to improve mood. In the US study referred to above, those on the high Se (226.5 mcg/d) diet significantly improved in the clearheaded/confused, confident/unsure and composed/anxious sub-scores, and total mood disturbance was significantly less.⁴¹ The results of this study are represented pictorially in Fig. 1, as the ratio of mean mood scores (six categories) in weeks 11-14 to those in weeks 2-5, for both the high and low Se diets. A similar finding was obtained in a double-blind crossover study carried out in the UK, where a 100 mcg Se supplement significantly decreased anxiety, depression and tiredness,⁴² the effect being most

marked in those consuming lesser amounts of dietary Se.

Thyroid function

Although it is recognised that deiodinase activity is relatively protected in conditions of marginal Se availability,¹ there are some indications that nonetheless, European levels of Se intake may compromise thyroid hormone-metabolism. For example, plasma T3:T4 ratios in young Scottish subjects were as low as those normally found in elderly populations.⁴⁴ Furthermore, Se supplementation in a small group of elderly subjects decreased plasma thyroxine (T4) levels, consistent with increased deiodinase activity and improved conversion to the active hormone, T3.⁴⁵ A combination of Se and iodine deficiency exacerbates hypothyroidism and may manifest itself as myxoedematous cretinism, such as is seen in the Democratic Republic of Congo (Zaire) where deficiencies of both these minerals exist.⁴⁶

Cardiovascular Disease

There is some evidence to suggest that selenium may be protective against cardiovascular disease.⁴ On theoretical grounds, this is supported by the ability of GPx to combat the oxidative modification of lipids and to reduce platelet aggregation.⁴ GPx4 has been shown to reduce hydroperoxides of phospholipids and cholesteryl esters associated with lipoproteins⁴⁷ and may therefore reduce the accumulation of oxidised low-density lipoproteins in the artery wall. GPx is required for the metabolism of hydroperoxides produced in eicosanoid synthesis by the lipoxygenase and cyclooxygenase pathways.⁶ In Se deficiency, a build up of these hydroperoxides inhibits the enzyme prostacyclin synthetase which is responsible for the production of vasodilatory prostacyclin by the endothelium, but stimulates the production of thromboxane which is associated with vasoconstriction and platelet aggregation.⁴ The balance is therefore tipped towards the pro-aggregatory state. In men with coronary artery disease, platelet aggregability has been shown to be inversely related to Se status.^{4,48}

Prospective epidemiological studies have had mixed findings. While Salonen and colleagues found a two to three-fold increase in cardiovascular morbidity and mortality for subjects with serum Se levels < 45 mcg/L compared to subjects above that level at baseline,⁴⁹ Virtamo's group found no significant associations with Se levels above and below that cut-off point except for stroke mortality.⁵⁰ A recently published study by Suadicani et al. showed that middle-aged and elderly Danish men with serum Se < 79 mcg/L had a significantly increased risk of ischemic heart disease.⁵¹ However, about half a dozen other studies have not shown a clear association between cardiovascular risk and low Se, though these differ from the above in having included few or no subjects with low Se levels.^{4,52} That a low Se status may be relevant was suggested by the findings of Kardinaal and colleagues in the 10-centre EURAMIC study where a significant inverse association between toenail Se levels and risk of myocardial infarction was shown only for the centre with the lowest Se (Germany).⁵³ Thus the effect may only be apparent in populations of low Se status, lower than the levels obtaining in the US and a large part of Europe. The disparity between studies may also be explained to some extent by the status of other antioxidants such as vitamin E, which may compensate for a deficiency in Se in protection against atherosclerosis.⁵³

A further factor to be taken into consideration when assessing these studies is that atherosclerosis is an inflammatory state and will provoke the acute phase response to a degree related its severity. Being an acute phase reactant,⁵⁴ some fall in plasma Se concentration might be expected in subjects suffering from atherosclerosis, even before the occurrence of an event.

Other oxidative-stress or inflammatory conditions

Se behaves both as an antioxidant and antiinflammatory agent. This is because Se in its

antioxidant role, notably as GPx, can (i) reduce hydrogen peroxide, lipid and phospholipid hydroperoxides, thereby dampening the propagation of free radicals and reactive oxygen species; (ii) reduce hydroperoxide intermediates in the cyclooxygenase and lipoxygenase pathways leading to inflammatory prostaglandins and leukotrienes and (iii) modulate the respiratory burst, by removal of hydrogen peroxide and superoxide.⁶

Any condition associated with increased levels of oxidative stress or inflammation might be expected to be influenced by Se levels. There is some evidence that this is the case in rheumatoid arthritis (RA), pancreatitis and asthma.

In a case-control study nested within a Finnish cohort of 18,709 men and women who had no arthritis at baseline, the adjusted relative risk between the highest and lowest tertiles of serum Se were 0.16 (95% CI 0.04-0.69; P for trend 0.02) for rheumatoid-factor(RF)-negative arthritis. There was no association for RF-positive RA.⁵⁵ In a double-blind randomised controlled trial in a small group of RA patients, supplementation with 200 mcg Se as Se-yeast for 3 months, gave a significant reduction in pain and joint involvement.⁵⁶

There is evidence for a protective effect of Se in pancreatitis, a condition associated with a high level of oxidative stress. At Manchester Royal Infirmary, administration of Se (600 mcg/day) along with other antioxidants to patients with chronic and recurrent pancreatitis, significantly reduced pain and frequency of attacks. Treatment has been revolutionised by obviating the need for surgery for pancreatic pain.⁵⁷ Se has also shown benefit in acute pancreatitis. In a small controlled trial carried out in Rostock in Germany, intravenous administration of Se to patients suffering from acute necrotizing pancreatitis, reduced mortality from 89% in controls to 0% in the treatment group.⁵⁸

With regard to asthma, a protective relationship was found between dietary Se intake and asthma in adults in a large population-based case-control study in London (OR 0.84 per quintile increase; 95% CI 0.75-0.94; P = 0.002).⁵⁹ In a small nested case-control study, current wheeze among New Zealand children was found to be more common in those with low levels of Se in serum samples collected eight-years previously (OR 3.1; 95% CI 0.9-11.8).⁶⁰ Another small study in intrinsic asthmatics showed significant clinical improvement upon supplementation with Se at 100mcg/d as sodium selenite.⁶¹

Se supplementation may be of benefit in preventing ischemia-reperfusion injury: a Se-enriched diet had a significant effect (P < 0.05) in preventing reperfusion-induced arrhythmias in an animal model.⁶²

Cancer

There is a considerable body of evidence showing a protective effect of Se against cancer. A number of epidemiological studies carried out since the 1970s have provided evidence of an inverse relationship between Se intake and cancer mortality. In a study carried out by Schrauzer,⁶³ dietary intake of Se in 27 countries was found to correlate inversely with total age-adjusted cancer mortality, while in an investigation of the relationship between forage-crop Se and county levels of cancer mortality in the US, cancer mortality rates for the major cancer sites were found to be significantly higher in low Se counties.⁶⁴

In prospective studies published in the '80s and early '90s involving from 8-11,000 subjects, low Se status was associated with a significantly-increased risk of cancer incidence and/or mortality. Risk has been from two-fold to six-fold higher in the lowest tertile or quintile (according to the study) of serum Se concentration,^{65,66} though in one case,⁶⁶ the effect was only apparent among males.

Later studies have reinforced the beneficial effect of higher Se status. A nested case-control study within a cohort of 9,000 Finnish individuals showed the adjusted relative risk of lung cancer between the highest and lowest tertiles of serum Se to be to be 0.41 (95% CI 0.17-0.94).⁶⁷ In the case of hepatocellular carcinoma (HCC), a significant inverse association

was shown between Se levels in stored plasma and later development of the disease in a cohort of 7,342 Taiwanese men, with chronic hepatitis-virus (B or C) infection, a noted risk factor for the development of this condition (see below).²²

A prospective study commented upon in the pages of this journal in 1998,⁶⁸ involved 34,000 men from the Harvard-based Health Professionals' Cohort Study. Those in the highest quintile of Se status, as measured by toenail Se, were found to have only one third the risk of developing advanced prostate cancer of those in the lowest quintile (OR 0.35; 95% CI 0.16-0.78; P for trend 0.03). Only cases diagnosed more than two years after collection of the samples were counted.

There have been few intervention trials using Se as a single agent. A number of these have been carried out in China where HCC is the third highest cause of cancer mortality. There are several hot-spots where the incidence of HCC is particularly high. One of these is the Qidong county, around 40 miles north of Shanghai. In this region around 15% of adults carry the Hepatitis B surface antigen and these people are 200 times more likely to develop HCC. In a study where 226 Hepatitis B antigen carriers were randomised to either 200 mcg of Se yeast or placebo, no case of HCC occurred in the supplemented group after four years, while seven subjects in the placebo group had developed HCC.²¹

In another study, 130,000 people from five townships were recruited. The people of one township had their salt fortified with Se as sodium selenite (at 15 mg/Kg). The other townships had unfortified salt. After six years the incidence of HCC had fallen by 35% in the supplemented township while remaining unchanged in the control townships.²¹

The Nutritional Prevention of Cancer (or NPC) Trial, carried out by Clark and co-workers in the US, was the first double-blind, placebo-controlled, intervention trial in a western population, designed to test the hypothesis that selenium supplementation could reduce the risk of cancer.⁶⁹ In 1312 subjects with a history of non-melanoma skin cancer who were randomised to placebo or 200 mcg Se/day (as Se-yeast), although there was no effect on the primary end-point of non-melanoma skin cancer, those receiving Se showed secondary end-point effects of 50% lower total cancer mortality (RR 0.5; 95% CI 0.31-0.80; P = 0.002) and 37% lower total cancer incidence (RR 0.63; 95% CI 0.47-0.85; P = 0.001) with 63% fewer cancers of the prostate, 58% fewer cancers of the colon and 46% fewer cancers of the lung.

Analysis of treatment effect in Clark's trial by initial plasma selenium status, showed that the strongest treatment effect was observed in subjects in the lowest tertile of plasma Se i.e. those whose plasma Se level was <106 mcg/L at entry to the trial (see Table 2).⁷⁰ Selenium supplementation reduced the risk of cancer in this tertile by 48%.

Plasma or serum selenium concentrations (more or less equivalent) measured within the 1990s in a selected number of European locations are shown for comparison in Fig. 2. The upper level of the bottom tertile in the NPC trial is marked on the figure and it is apparent that these locations fall well within that tertile. Consequently, it might be predicted that a repeat of the NPC trial in these European locations would show a very marked treatment effect.

The NPC trial was carried out in a region where dietary selenium intake is 90 mcg/d,⁶⁹ low in US terms, but already well above the level required to optimise selenoenzyme activity.⁷¹ While this does not preclude a role for the selenoenzymes in cancer prevention, it suggests the operation of additional important mechanisms. Thus the anticancer effect of Se may relate more closely to its ability to enhance the immune response or more probably, to its ability to produce anti-tumourigenic metabolites (e.g. methyl selenol or its precursors) that can perturb tumour-cell metabolism, inhibit angiogenesis and induce the apoptosis of cancer cells.⁶⁵ In this context, there is considerable current interest in defining the species of Se present in selenium yeast (of which the major proportion is believed to be selenomethionine)

with a view to identifying the most active anticarcinogenic component.

Current selenium intake and status in the UK and Europe

Se intakes in most parts of Europe are considerably lower than in the US, soils in the US being a better source of selenium.⁷²

Recent Se intake levels in some European countries are shown in Table 3. When considering the adequacy or otherwise of these levels, we need to have appropriate standards against which to compare them. There is no consensus on this issue. The UK RNI (Reference Nutrient Intake) of 75mcg/d for men and 60 for women has been determined as the level of intake believed to be necessary to maximise the activity of the antioxidant selenoenzyme GPx in plasma,⁴³ which has been found by a number of workers to occur at a plasma concentration of around 100mcg Se/L.⁷¹ Current UK intakes are only about half the RNI, having declined considerably over the last 25 years.⁷³ The significant inverse correlations found between baseline selenoenzyme activities in UK subjects and percentage change in activity upon supplementation, suggests sub-optimal enzyme activity at the current level of intake.⁷⁴ This may have implications for normal cell metabolism and disease risk,⁷⁴ not only in the UK, but in other European countries with intake levels in the same range (see Table 3).

The US RDA (Recommended Dietary Allowance), which is the most widely quoted standard, has been set similarly at 70mcg/d for men and 55 for women, on the basis of optimisation of plasma GPx activity⁷¹ in Chinese subjects in Keshan Disease areas, with appropriate body-weight and safety-factor corrections for US subjects. However a WHO/FAO/IAEA expert group, working from the same Chinese data, recommended an intake level of only 30mcg/d for women and 40 for men, on the arbitrary basis that only 2/3 of the full expression of GPx activity was required.⁷⁵ It should be noted that these recommended intakes are based on a small supplementation study where Se of good bioavailability (selenomethionine) was administered to subjects whose excretion patterns were well adapted at the outset to Se conservation.⁷¹ If the requirement of saturation of GPx activity in the platelets, rather than the plasma, is used as the measure of Se repletion, then a higher level of intake is needed, i.e. around 80-100mcg/d.⁷⁶

When considering requirements, the following factors should be borne in mind:- the form of Se ingested affects the response of the selenoenzymes;⁷⁴ adaptation to low Se intake can occur by sparing excretion;⁷¹ there is significant ($P < 0.001$) inter-individual variation in the extent of the response of the selenoenzymes to supplementation, therefore requirements will differ between individuals in the same population.⁷⁴

At low, or relatively low, levels of Se intake, a good correlation exists between serum/plasma Se and erythrocyte GPx activity.¹⁰ At higher intakes, GPx activity reaches a plateau.¹⁰ With the caveats mentioned above, serum/plasma Se is therefore a useful marker of status in populations with a low, or relatively low, level of intake. This situation applies in a number of European locations (Fig. 2) where serum/plasma Se concentrations are below the level required for saturation of GPx activity.⁷¹ It seems, though, that levels of Se intake that saturate the activity of plasma GPx, while satisfying the enzymic or antioxidant role of Se, are insufficient to optimise the immune response, and reduce cancer risk. This insufficiency would be even more marked were we to accept levels of Se intake that give only 2/3 of the full expression of GPx activity.

A new functional marker of Se status is currently being sought, representative of biologically-effective levels. However Se has diverse biochemical roles. These different roles may require a range of markers of status according to the function, or disease, under investigation. A number of selenoenzymes are candidates for functional markers. It is

unlikely, however, that these will be appropriate for roles of Se that relate, for instance, to the production of anti-carcinogenic Se metabolites.

Sources and bioavailability of selenium

With the exception of Brazil nuts (which are said to accumulate radioactive barium) and kidney, there are few good food sources of Se in many European countries. Crab, liver, other shellfish and fish are moderately good sources, though studies show marked differences in the ability of Se from fish to increase parameters of Se status.^{77,78} (The existence of different Se compounds in fish, their dependence on fish species or source, or interaction with mercury or arsenic, known contaminants of fish, may explain this disparity.^{77,78}) Many people rarely eat foods which are good sources of Se. In N. America, wheat is a good source but the same cannot be said for European wheat because of low availability of Se in most European soils.⁷² Despite that, bread and cereals, being commonly consumed, make a substantial contribution to Se intake in northern Europe (around 22% in the UK⁴³). Meat, poultry and fish make the biggest contribution (approximately 36% in the UK⁴³). Se consumed in foods and supplements exists in a number of organic and inorganic forms including selenomethionine (plant and animal sources and supplements), selenocysteine (animal sources), selenate and selenite (mainly supplements). Bioavailability and tissue distribution depend on the form ingested. For instance, selenomethionine is more effective in increasing apparent Se status because it is non-specifically incorporated into proteins (e.g. haemoglobin, albumin) in place of methionine.⁷¹ However it has no catalytic activity there and must be catabolised to an inorganic precursor before entering the available Se pool. It is a less-available metabolic source of Se than selenite or selenate, as these need only be reduced to selenide to provide selenophosphate, the precursor of selenocysteine, the active form of Se in selenoproteins.² Despite this, organic forms e.g. high-Se yeast, are often preferred in interventions, partly because they are less acutely toxic. They may, however, be *more* toxic during long-term consumption, owing to non-specific retention of Se as selenomethionine in body proteins, rather than its excretion.

Interaction with toxic metals in the food supply

Se seems to reduce the toxicity of a number of metals by forming inert metal selenide complexes. Mercury or methyl mercury in marine foods is found combined with selenium which may protect against mercury toxicity.¹⁰ This may, incidentally, reduce the bioavailability of Se from such foods (see above).

Selenium research - the way ahead

The last five years of the 20th century have been an exciting time in Se research and this trend seems set to continue, at least for some time.

The previously-unsuspected role of host Se status in the emergence of viral disease promises some new strategies for prevention and treatment.^{15,18} Elucidation of the importance of novel viral selenoproteins may improve our understanding of HIV.¹⁴ Baum's group is currently running two double-blind, placebo-controlled, randomised clinical trials on Se supplementation of HIV-positive individuals: one in a cohort of 100 children from the Dominican Republic which should provide results within the year 2000; the other in 350 drug users in Miami, scheduled to finish towards the end of 2002. Survival is the primary-outcome measure.

With regard to cancer, an extended repeat of the NPC trial is now planned with

cohorts in three European countries and the US, to see if the reduction of cancer risk and mortality with selenium supplementation previously observed can be replicated in other population groups. Baseline plasma selenium levels in these European countries, the UK, Denmark and Sweden would fall clearly into the bottom tertile of the NPC trial as outlined above. This new trial, the PRECISE trial (PREvention of Cancer by Intervention with SEelenium), will recruit around 33,000 European subjects of whom 11,000 will be from the UK, where the author is the cohort leader. Pilot studies have already begun in the UK and Denmark. As an adjunct to the 500 subject UK pilot, the effect of Se supplementation on mood and quality of life is being investigated.

Furthermore, the US National Cancer Institute has agreed to fund the 14-year SELECT trial, where 32,000 men will be recruited to ascertain the effect of supplementation with Se, (200 mcg as selenomethionine) and vitamin E, on the risk of prostate cancer, in a 2x2 factorial design.

In this context, it will be interesting to see whether the 15 kDa selenoprotein found in the glandular epithelial cells of the prostate⁹ is implicated in the apparently-protective effect of Se against carcinoma in this organ.

Conclusions

Recent evidence has reinforced the importance to health of adequate selenium status. Research suggests that selenium intakes may be sub-optimal with respect to disease risk, notably in populations of adults in the UK, parts of Europe and New Zealand and even in the US. Indications that this may be the case are strongest for cancer, where Se intake at a considerably higher level than that required to saturate the selenoenzymes would appear to be beneficial, and HIV progression to AIDS. Further research is needed to clarify the optimal nutrition level with respect to selenium. In this context, the planned PRECISE and SELECT trials should give the definitive answer on the ability of selenium to reduce cancer risk.

If similar results were to be obtained to those of the NPC trial, addition of Se to the food supply in countries such as the UK, would be a possible outcome. This has been achieved in Finland, where Se intakes were formerly very low, by addition of Se to fertilisers since 1984.

A word of warning however is in order: while awaiting the results of PRECISE, SELECT and other clinical trials, we must be careful not to encourage the overconsumption of Se supplements. While an intake of Se of around 15 mcg/kg body-weight/day is thought to be without prolonged impact on human health, it must be remembered that Se is a toxic mineral with a relatively small therapeutic window. In some sensitive individuals, the maximum safe dietary intake may be as low as 600 mcg/day.⁷⁹ It would therefore seem prudent to restrict adult intake from all sources to 400-450mcg/d, as recommended by a number of expert panels.⁷⁵

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Selenoprotein	Function
Glutathione peroxidases (4) (GPx1, GPx 2, GPx 3, GPx 4)	Antioxidant enzymes: remove hydrogen peroxide, lipid and phospholipid peroxides (thereby maintaining membrane integrity, modulating eicosanoid synthesis, modifying inflammation and the likelihood of propagation of further oxidative damage to biomolecules such as lipids, lipoproteins and DNA). ^{1,2,3,6}
(Sperm) mitochondrial capsule selenoprotein	Form of glutathione peroxidase (PHGPx): shields developing sperm cells from oxidative damage and later polymerises into a structural protein required for stability/motility of mature sperm. ⁷
Iodothyronine deiodinases (3)	Production and regulation of level of active thyroid hormone, T3, from thyroxine, T4 ¹
Thioredoxin reductases (3)	Reduction of nucleotides in DNA synthesis; maintenance of the intracellular redox state, critical for cell viability and proliferation; ² regulation of gene expression by redox control of binding of transcription factors to DNA ²
Selenophosphate synthetase, SPS2	Required for the biosynthesis of selenophosphate, the precursor of selenocysteine, and therefore for selenoprotein synthesis ²
Selenoprotein P	Found in plasma and associated with endothelial cells. Appears to protect endothelial cells against damage from peroxynitrite. ^{1,2,8}
Selenoprotein W	Needed for muscle function ^{1,2}
Prostate Epithelial Selenoprotein (15kDa)	Found in epithelial cells of the ventral prostate. Seems to have a redox function (resembles PHGPx), perhaps protecting secretory cells against development of carcinoma. ⁹
DNA-bound spermatid selenoprotein (34 kDa)	Glutathione peroxidase-like activity. Found in stomach and in nuclei of spermatozoa. May protect developing sperm. ⁹
18 kDa selenoprotein	Important selenoprotein, found in kidney and large number of other tissues. Preserved in Se deficiency. ⁵

Table 1: Known selenoproteins that carry out the nutritional functions of Se

Baseline plasma Se (mcg/L)	Se cases	Placebo cases	RR*	95% CI**	P-value
<106	28	56	0.52	0.33, 0.82	0.005
106-121	34	49	0.64	0.40, 0.97	0.40
>121	45	41	1.00	0.65, 1.54	0.99

* relative risk

** 95% Confidence Interval

Table 2: Total cancer incidence 1983-96 by plasma Se level at baseline

Country	Intake (mcg/d)	Information source
UK	29-39	UK Ministry Agriculture, Fisheries, Food 1997
Belgium	28-61	Robberecht and Deelstra 1994
France	29-43	Lamand et al. 1994
Germany (Bavaria)	35	Kumpulainen and Salonen 1996
Netherlands	67	Kumpulainen 1993
Denmark	38-47	Danish Government Food Agency 1995
Sweden	38	Kumpulainen 1993
Switzerland	70	Kumpulainen 1993
Poland	11-24 (estimate)	Kvícala et al. 1995, 1997
Slovakia	38	Kadrabova 1998

Table 3: Recent Se intake levels in some European countries

These are the sources of the values used to construct the Fig. 2 bar chart. ***N.B. This is not intended to be included in the text of the paper.***

Some recent serum/plasma Se values in Europe (mcg/L)

McMaster 1993 72.6 Strasburg 248 subj	McMaster 1993 75.8 Toulouse 220 subj	McMaster 1993 78.2 Lille 228 subj
Simonoff et al 1993 83 (TEMA 8) Bordeaux 25 controls	Coudray 1997 86.86 Nantes 1389, 59-71y	Girelli et al 1992 84.6 Verona 45 healthy bl. donors, 35M 10F
Bellisola et al 1993 64.7 Veneto, NE Italy 82 normals	Olivieri et al 1994 86.6 Veneto, Italy	Gerli 75 Milan 50 subj. age 22-59
Fernandes-Banares 1990 60.01 Spain 105 healthy subj, all ages	Cabre 1992 61.6 Barcelona 83, mean age 36	Van Cauwenbergh 1994 68.8 160 urban Greek bl donors Age 18-50
Tiran et al 67.2 Austria	Grandjean et al 1992 83.7 Odense, Denmark	Lassen & Horder 1994 75.2 Odense, Denmark
Winnefeld et al 1995 81.3 Jena, Germany 100 bl. donors	Wang et al 1995 86.1 127 Swedish orienteers, age 17-30	Korunova 1993 74 Czech rep. 367 subj.
Scieszka et al 1997 51.4 Upp. Silesia, Poland	Gondi 1992 55.9 (weighted mean) Hungary (E/N/S) 140 subj	Maksimovic 1992 50 Yugoslavia 875 subj. M/F
Maksimovic 1991 43.2 Serbia 449 subj. 20-50	MacPherson et al 1995 72 Scotland	Barrington et al 1997 76.6 Wales women
Shortt et al 1997	MacPherson et al 1998	

60.44
Scotland, M & F

79.21
Scotland