The Role of Minerals and Trace Elements in Relation to Long-Term Health and Chronic Disease

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Introduction

By definition, all of the major minerals and essential trace elements are necessary for health, and the range of these elements implies that they are part of all aspects of cellular function. They are involved as structural components, such as calcium or phosphorus in bone, as cofactors for enzyme activity or as an integral part of enzyme or protein structure (metalloproteins). They influence all metabolic pathways, are part of the antioxidant systems to prevent oxidative damage to cells, and are part of control mechanisms in the cell such as the zinc finger transcription factors. The breadth of this topic is extremely wide, and hence the current discussion will be limited only to nutritional deficiency states and their effects, and to examples selected from three key minerals (calcium, phosphorus, and magnesium), and from the well-established trace elements (iron, zinc, copper, selenium, chromium, molybdenum, manganese, cobalt and iodine).

The ‘classical’ way of describing the progressive development of a nutritional deficiency state is shown in figure 1. When dietary supply is inadequate, the body will first mobilize any stores, if available, e.g. calcium will be mobilized from bone. Thereafter there will be an attempt to compensate either by increasing absorption from the gut, e.g. for iron, or reducing urinary excretion, e.g. for magnesium or phosphate. If the inadequate supply continues, or if there is no effective homeostatic mechanism, cellular deficiencies will occur which will have a wide range of effects on metabolism, depending on the element and the tissues mainly involved. These cellular effects may be apparent in some change in metabolism, e.g. chromium deficiency and glucose intolerance in type-2 diabetes, or magnesium deficiency and hypocalcemia. Signs and symptoms may be fairly nonspecific at this time – fatigue, mental and cognition changes,
or immune changes. Eventually, and after a period that may vary from a few weeks to months or years, signs and symptoms of disease will develop. This will depend on the element concerned, the normal daily requirement, and the severity of the deficiency.

Although in some ways it is easier to undertake a review in which each element is considered in turn, with the biochemical, physiological and pathological changes associated with each deficiency being discussed in succession, for the purposes of the present discussion, certain disease states have been selected for review because of current controversy or the potential importance of particular elements in the disease state.

**Osteoporosis**

Osteoporosis is a common systemic skeletal disease, which is characterized by low bone mass and disturbed micro-architecture, leading to an increased
susceptibility to fracture. After the age of 50, women have a 40% lifetime fracture risk, whereas for men the figure is 14% [1]. The incidence of fractures is increasing worldwide, partly due to the ageing population and partly to changes in lifestyle, especially the reduction in exercise. The main factor in determining fracture risk is bone mineral density (BMD), which can account for about 75% of the risk [2]. BMD may be low in the elderly either due to a low peak bone mass being achieved during early adult life, to an increased rate of bone loss, or to both of these.

The most important factors in determining peak bone mass are genetic, including body size and composition, and various polymorphisms for vitamin D and estrogen receptor genes [3]. Nutritional factors probably only account for 20–30% of the peak bone mass, but nonetheless this is important. Calcium intake and exercise are of key importance, and the reference nutrient intake for calcium in the UK has been set at 1,000 mg for adolescent males, and 800 mg in females, falling slightly to 700 mg thereafter [4]. There remains some controversy regarding the optimal intake of calcium, especially since the publication of the USA National Institutes for Health Consensus Panel report [5], which proposed intakes of about 1,500 mg/day, much higher than both the USA and UK reference values. As discussed in detail in the UK review [4], and in the subsequent Food and Nutrition Board review [6], the evidence is lacking to support the proposed optimal values to maximize peak bone mass, to maintain adult bone mass, and to minimize bone loss, and therefore at present only adequate levels of intake are quoted in the dietary reference values.

Other nutritional factors which may be relevant in achieving a good peak bone mass include protein intake, which is associated with an increase in BMD during the prepubertal growth spurt, and the increase in insulin-like growth factor-1 in response to increasing protein intake.

The main cause of bone loss in women is the reduction in circulating estrogen as a result of the menopause. The resulting increase in bone turnover is accompanied by a reduced rate of bone formation, making bone loss inevitable. This is exacerbated by genetic factors, by reduced intestinal absorption of vitamin D, by reduced dietary calcium, and by reduced physical activity, all of which accelerate bone loss.

Vitamin D is of particular importance in maintaining bone health. It plays a key role in increasing absorption of calcium from the diet, and in mobilizing calcium from bone when the serum concentration falls. In the presence of inadequate vitamin D, either through dietary lack or inadequate exposure to sunlight, calcium absorption falls, the serum concentration of calcium also falls, leading to a feedback increase in parathyroid hormone (PTH) secretion, increased bone turnover, and bone loss, eventually leading to osteomalacia [1].

Can Mineral Supplements Improve Bone Health?

There is some evidence that calcium supplements alone may improve bone density, but the results have not been consistent. In one study [7], the
beneficial effect of calcium supplements was limited to those with daily calcium intakes of less than 400 mg/day, but even this finding is not consistent. Similarly, there are variable results using fracture as the clinical endpoint. Case-control studies in the UK, Australia, and Canada have shown no relationship between calcium intake and the risk of hip fracture, whereas similar studies in Hong Kong and southern Europe suggest an increased risk of hip fracture with lower calcium intake [4].

However, there is convincing evidence that a combination of calcium and vitamin D will reduce the incidence of non-vertebral fractures. For example, Chapuy et al. [8] found that a supplement of 1,200 mg Ca with 20 μg vitamin D/day over a 3-year period led to a reduction in hip fractures of 29%, and in other non-vertebral fractures of 17% in a study of 1,765 elderly institutionalized women. These results have been confirmed in a more recent study in USA [9].

The role of phosphate in osteoporosis is less well investigated. However, some interesting studies by Fraser et al. [10] have investigated the relevance of the circadian rhythm of phosphate and PTH. In normal premenopausal women, or postmenopausal women without osteoporosis, there is a nocturnal increase in both phosphate and PTH from 2,200 to about 700 h. In patients with postmenopausal osteoporosis, the nocturnal rise in PTH is absent and instead it decreases steadily throughout the night, and there is an absence in the nocturnal rise in phosphate in most individuals. Since the PTH changes tend to follow the phosphate changes, and intermittent PTH injection is associated with an increase in bone formation markers, phosphate intake from meals or, if given therapeutically, may have a role in controlling PTH levels and altering bone mass. Further studies are needed in this area.

There is also interest in the possible link between acid-base metabolism and bone health, and the observation that the intake of foods such as fruit and vegetables that are rich in the alkaline elements, potassium and magnesium, may be associated with higher BMD [11]. Dietary magnesium correlates with reduced excretion of markers of bone resorption, implying better biochemical status and improved bone mass in adults [12], and urinary potassium is positively correlated with bone mass in children. On the other hand, a diet rich in sodium has been associated with increased urinary calcium loss and concomitant bone loss [13].

There is also strong theoretical evidence, and some experimental evidence for a role for zinc and copper in bone health [14]. Zinc is an essential cofactor for the enzymes of nucleic acid and protein synthesis, and retardation of bone growth is commonly found in zinc deficiency. In bone, zinc plays roles in the structure of the bone matrix, in the stimulation of bone formation by osteoblasts, and inhibition of resorption by osteoclasts. Copper is a cofactor for lysyl oxidase, which is involved in the formation of lysine-derived cross-links in collagen, an essential part of the bone matrix.
There is limited evidence of value in supplementing copper and zinc in postmenopausal women. One trial of copper alone led to no loss of BMD in the supplemented group, but a significant decrease in BMD in the placebo group [15]. In a small trial, a combination of calcium, zinc, manganese and copper was found to improve spinal BMD [16]. Clearly further studies are required on the effects of these trace elements.

**Conclusions**

Osteoporosis is a multifactorial disease primarily affecting postmenopausal women. Nutrition is only one part of its complex etiology and management. However, optimization of calcium status together with vitamin D is already an important part of therapy, and it can be anticipated that future research will clarify the optimal intake of the major minerals potassium, sodium, phosphorus and magnesium, and of the trace elements zinc and copper.

**Immune Function**

It is self-evident that minerals and trace elements will be essential for the effective operation of all aspects of the immune system. The active oxidative metabolism of neutrophils as part of chemotaxis and phagocytosis, clonal differentiation of lymphocytes, and receptor expression and antibody synthesis all require integrated action of many enzymes in which these elements are either essential cofactors, or are part of the prosthetic group [17]. Most elements have been thoroughly investigated in a variety of in vitro systems, and some of the effects are summarized in table 1. Zinc in particular is recognized as having a plethora of effects on both T and B lymphocytes.

One of the difficulties in this field is attempting to extrapolate in vitro findings to the in vivo situation. In other words, what are the clinical consequences
of a suboptimal status of a particular element? This is complicated by two major problems: firstly, that most deficiencies in man are multiple, and hence it is difficult to clarify the effect of a single element deficiency on the incidence of infection, and secondly, that as a result of this knowledge, most clinical trials have used multiple micronutrients, usually a complex of all essential trace elements and vitamins, and hence any benefit cannot be ascribed to any one vitamin or trace element. There are however a small number of studies, which help to demonstrate the specific importance of optimizing trace element intake to reduce the risk of infection and its complications.

**Studies in Healthy Elderly**

Girodon et al. [18] performed an important study in 725 institutionalized elderly subjects (mean age 83.9 years) from 25 geriatric centers in France. This was a prospective, randomized placebo-controlled trial of the effects of trace elements (zinc plus selenium), vitamins (β-carotene, ascorbic acid, and vitamin E), or trace elements plus vitamins, over a 2-year period. The proportion of patients remaining free from infection throughout the period was higher in the trace element group than in the other 3 groups, but there was no significant difference in terms of the total number of infections. Interestingly, in a small subgroup of 80 patients from 1 nursing home, the trace element group had a reduced number of respiratory and urogenital infection than the other groups, which may reflect particular nutritional deficiencies in this group of patients [19]. However, it should also be noted that in a large subset of all the patients studied, the antibody response to influenza vaccine was significantly better in the trace element group than in the group receiving vitamins. The vitamin supplements appeared to have a negative effect on the antibody response at 28, 90 and 270 days after vaccination (fig. 2). If these results are repeated, this might suggest that it is important to provide only the supplements patients require to correct for inadequacies in the diet. In some populations, a zinc and selenium supplement may be more effective than a standard complete vitamin and trace element multinutrient tablet.

There are few other studies on healthy elderly of sufficient size or quality to reach confident conclusions that there is any beneficial effect on the incidence of infections of trace elements alone, or indeed in combination with vitamins.

**Childhood Infections**

The role of zinc deficiency on diarrhea in children in developing countries has been extensively studied. Although the pathophysiology of diarrhea is complex, often being due to a combination of infective and non-infective effects, provision of zinc is effective in reducing the probability of continuing diarrhea [20]. There is more limited data suggesting that the incidence of lower respiratory tract infection and clinical attacks of malaria may also be reduced by zinc supplementation in these populations [21].
In a study of tuberculosis in Indonesia, supplementation with zinc and vitamin A led to much earlier resolution of X-ray changes and time to sputum negativity [22].

The interaction between zinc and vitamin A has been examined by Rahman et al. [23]. In a study of 800 children in Bangladesh, a supplement of zinc, vitamin A, a combination of both, or placebo was given for 2 weeks to children who were then followed up for 6 months. Combined zinc and vitamin A synergistically reduced the prevalence of persistent diarrhea and dysentery. However, zinc alone was associated with a significant increase in acute lower respiratory infection, but this adverse effect was reduced by the interaction between zinc and vitamin A. This would again tend to suggest the importance of providing supplements to correct existing deficiencies, and that partial correction, or unbalanced correction may be harmful.

**Selenium Deficiency and Virulence of Infection**

Although not directly relating to immune function, another line of investigation has potential consequences on the incidence of infection. This is the observation that when a normally benign strain of Coxsackie B3 virus is injected into selenium-deficient mice, the virus mutates to a more virulent form which may cause severe cardiomyopathy [24]. The viral genome was found to have mutated in 6 regions when the virus was cultured at the end of the study. The same group has also demonstrated that influenza virus causes more severe lung pathology in selenium-deficient mice, probably also as a result of genome mutation; they identified 29 nucleotide changes in the M1 matrix protein, an internal viral protein [25]. The relevance of these findings to human infectious disease remains to be established, but if there are comparable effects in man, there are implications for optimization of selenium status.
HIV Infection and AIDS

Weight loss is a common problem in HIV, and patients are frequently found to have abnormalities of plasma mineral and trace element concentrations, especially of zinc, selenium and magnesium [26]. There are a number of interacting factors, including loss of appetite, decreased absorption, diarrheal and urinary losses, and the effects of redistribution from plasma to tissues as a result of the response to infection [27].

Of special significance is the role of trace elements and other micronutrients in antioxidant defense. Zinc and copper are essential for cytoplasmic superoxide dismutase, manganese for the mitochondrial enzyme, and selenium is part of the prosthetic group of glutathione peroxidase. Loss of antioxidant activity will lead to increased activation of NF-κB, which is a key regulator of HIV replication [28]. There is evidence that the decline in plasma selenium parallels the loss of CD4+ cells, and that low levels of selenium in children is related to faster disease progression and to mortality [29]. Although supplementation may lead to biochemical improvement, demonstrating that this leads to improved clinical outcome remains controversial.

The complexity of determining supplements is typified by iron. Some patients may develop iron deficiency anemia, whereas others have excess iron. Iron supplementation in HIV may be effective in treating iron deficiency anemia and also causes an increase in peripheral lymphocytes. However, excess iron supplements may stimulate oxidative stress, and induce an unhelpful Th2-type response. There is also evidence that iron chelation may have antiviral effects on HIV [30]. Again, this would suggest the value of correcting iron deficiency, but not providing supplements to those who do not require them.

Apart from the direct effect on the progress of the illness in the patient, there is also evidence of the importance of selenium status in transmission. Patients with selenium deficiency (defined as 85 μg/l, 1.1 μmol/l, results which are in the middle of the UK reference range) were found to be nearly three times as likely to have vaginal shedding of HIV-infected cells [31]. However, evidence of the benefit of supplementation is yet again still lacking.

Conclusions

There is much laboratory, theoretical and observational evidence that trace elements and minerals are important in optimizing aspects of immune function and that changes occur in disease. However, with the exception of studies in children, there have been few well-performed, large, long-term studies of supplementation, in the elderly or in particular disease states. This is partly because of the difficulty in performing such controlled trials where the only variable is the trace element in question. However, if progress is to be made in this field, such prospective trials are essential.
Minerals and Trace Elements in the Pathogenesis of Cancer

There is remarkably little good information on the role of trace elements and minerals in cancer. Two major reviews on all aspects of nutrition and development of cancer by the World Cancer Research Fund [32] and the Committee on Medical Aspects of Food in the UK [33] concluded that the lack of evidence only allows some tentative conclusions, especially for selenium, calcium, and iron.

Selenium and Cancer

There is growing evidence that low selenium intakes in the diet are associated with higher cancer risk. Comparisons of the lowest with the highest quintiles have shown 2–6 times the risk of various cancers, including lung, hepatocellular, colon and prostate [34]. This may relate to the known antioxidant activity of selenium, which may protect against mutation, as well as the effects on stimulating NK cells and cytotoxic T cells [35].

There have been a few intervention trials of the effect of selenium on the incidence of cancer. Some studies have demonstrated a reduced incidence of hepatocellular cancer in regions of China where the incidence is high [29]. The first trial in a Western population was the Nutritional Prevention of Cancer Trial [36] which investigated 1,312 patients with a previous history of non-melanoma skin cancer. A supplement of 200 μg selenium/day over several years led to a reduction in the total cancer incidence of 37%, prostate cancer 63%, colon cancer 58%, and lung cancer 46%. The strongest treatment effect was seen in subjects in the lowest tertile of plasma selenium concentration; the upper limit of this tertile is 106 μg/l, a level above that found in many European countries [29]. It is therefore of great importance that this trial be repeated in populations with lower typical selenium intakes from the diet, and hence lower plasma selenium concentrations. Such trials are currently underway in Europe.

Calcium and Cancer

There is some evidence that calcium might decrease the risk of colon cancer by binding free fatty acids and bile acids in the colon and hence diminishing mucosal proliferation. There is an association between the intake of calcium and the incidence of colorectal polyps and cancer. However, short-term studies of calcium supplements in patients with polyps have not been conclusive [33].

Iron and Cancer

A high-iron diet may increase the risk of development of colorectal and liver cancer. Free iron catalyses the production of hydroxyl radicals, which may then cause oxidative damage in the colon. In animal studies, a high iron intake can induce tumors, the incidence being reduced by intake of phytate, a calcium chelator.
Oxidative stress is recognized to be a key etiological factor in two of the major degenerative eye diseases, namely cataract and age-related macular degeneration. Cataract has particularly been studied in relation to the benefit of vitamin C supplements. The retinal pigment epithelium is rich in both zinc and copper, primarily in the form of superoxide dismutase. It might therefore be hypothesized that lack of zinc and copper might cause changes in the retinal pigment epithelium followed by death of the adjacent photoreceptor rods and cones, leading to age-related macular degeneration.

The Age-Related Eye Disease Study group reported the results from a large prospective double-blind placebo-controlled study across 11 centers in the United States [37]. The supplements were of vitamin C (500 mg) plus vitamin E (400 IU) plus β-carotene (15 mg), zinc (80 mg) plus low-dose copper (2 mg), or both of these. 4,629 patients were followed up for a mean period of 6.3 years. The important conclusions from this study were firstly that there was no significant difference in the development or progression of age-related cataract. However, there was a significant reduction in the development of age-related macular degeneration, the combination of antioxidants together with zinc being most effective and leading to a reduction of about 25% (fig. 3).

This is a particularly important study, since it is one of the few well-controlled, prospective studies that have clearly demonstrated the added benefit of trace element supplements.

**Fig. 3.** The probability of developing advanced age-related macular degeneration (AMD) in at least one eye of participants who received placebo, antioxidants (vitamin C, vitamin E, and β-carotene), zinc, or antioxidants plus zinc. Adapted from the Age-Related Eye Disease Study Research Group [37].
Conclusions

Any disease in which the pathogenesis or progress is associated with a disturbance in metabolism, either in local tissues and organs or systemically, will have consequences for trace element and mineral status. There is particular interest at present in how to optimize provision of these essential elements to reduce the incidence of disease, and to reduce the complications, severity or duration of a disease once it is established. Most clinical trials of the effects of diets or nutrients do not control for individual elements. Moreover, trials are complex and expensive because of the need for large study groups, often over many years. Since the nutritional intervention is a widely available and cheap element or its salt, there is little incentive for industrial funding, and the costs are often in excess of traditional national funding agency budgets. Hence, much of the evidence is based on epidemiological or case-control studies rather than prospective interventional trials. Nonetheless, there are a growing number of examples of clear clinical benefit from preventing clinical and subclinical deficiency states. Improvements in laboratory assessment, including tissue concentrations and an assessment of antioxidant status, may assist in identifying the most effective intakes for individual elements in relation to particular populations and diseases.

References

Minerals and Trace Elements in Disease


Discussion

Dr. Wasantwisut: I have a comment on the relationship of zinc and vitamin A in malaria. Recent findings from Papua New Guinea indicate that vitamin A supplementation is helpful in those subjects who have a low parasite count while zinc works better with those with higher parasite counts [1, 2]. Some of the work that is being done has to do with the stage of infection, also defining which trace element will be effective. This is something that we need to know more about in coming years. My second question has to do with the biochemical cutoff point of trace elements during infection. Infection affects many in this population, and it is very difficult particularly to define their status. Is what is given the right choice? In infection sometimes when therapy is given nothing happens and people say it doesn't do anything. When we look at a number of studies, this is a very confounding factor making it difficult to compare them.

Dr. Shenkin: I entirely agree. I cannot comment on your studies on malaria because I am not familiar with the data. But certainly as far as your second point is concerned, the difficulty in the biochemical assessment of the severity of a deficiency in a population which already has infection is well recognized. Most of the biochemical indexes used to establish the severity of a deficiency are affected by the infection itself, causing an acute phase response with cytokine production and then the redistribution of trace elements and vitamins such as vitamin A and vitamin C into tissues.

So you are absolutely right. We need better markers of deficiency in infection to make it possible to interpret the severity of nutritional depletion in that group of individuals who are already infected. It is exceptionally difficult.

Dr. Go: A key problem I have, if we were changing paradigms I would like to address the last two points you showed in your slide. I was wondering whether in fact there is a change of paradigm with research that needs to be done on trace minerals? We went to the stage of identifying one mineral or one vitamin for one disease, calcium for osteoporosis, selenium for cancer, but in reality it is not really one mineral or one vitamin. In reality it is similar to what Dr. Rock told us, it is in diet concoction. Perhaps we need to change our paradigm in chronic disease research, we may have to look at commonality in antioxidant properties in all vitamins and trace minerals in the prevention of chronic disease such as diabetes, osteoporosis, metabolic syndrome, and hypertension. So I am really suggesting we change the paradigm if we want to continue in this field of research.

Dr. Shenkin: I suppose the answer is yes and no. It would be nice to do that, and you are right that the studies which use multiple types of additives are probably easier to perform and they are more likely to lead to beneficial results overall. But I was very worried by a number of studies, particularly by the French study in nursing homes demonstrating that a relatively mild intake of vitamins appears to be harmful in certain groups for no particularly good reason, but that observation requires confirmation. But there are other studies of which you may be aware, especially the studies on β-carotene and cancer. Everyone was convinced of the potential benefits of β-carotene on the basis of epidemiological studies, but when trials were performed with β-carotene supplements, there was a higher rather than a lower incidence of lung...
cancer. So throwing everything together into one large pot, it may be almost impossi-
ble to interpret which are the good guys and which are the bad guys and to demon-
strate that conclusively. There has been a lot of interest in antioxidant benefits, with
the assumption that oxidative damage is bad and will lead to clinical disease. However,
proving this association has been very difficult. In heart disease, taking vitamin E
doesn't help nor does vitamin C. The clinical trials do not show benefits despite the
theory. I worry a little bit about the multi-supplements approach although single
supplements may be ineffective, and I think you need both approaches to try to unpick
the response to any mixture.

Dr. Angkatavanich: My first question is about the effects that you have shown on
your slides. I wonder if there is a separate effect of those outcomes that you presented
in terms of whether it is only the treatment of deficiency or is it the pharmacological
effect? In principle we have to separate it so that we can use the data clearly. Secondly,
in a study from the US I came across data showing that the effect of vitamin A was
even worse in infection. You showed data on the effect of zinc and vitamin A. Is there
any difference in terms of a reduction in the infection incidence comparing zinc plus
vitamin A and vitamin A alone?

Dr. Shenkin: As far as your first question is concerned: there have been a few
studies which might be called pharmacological as far as trace elements or minerals are
concerned because the therapeutic range of benefit is fairly narrow. For most trace
elements, if you take too much then you get toxic effects, for example selenium or
zinc. There is a much higher safety margin for water-soluble vitamins, for example vita-
minal C or vitamin E or some of the other vitamins. But when we are talking about min-
erals it would be surprising to have what you might call a pharmacological effect as
opposed to a nutritional effect. On the other hand, the cancer study from United States
used an intake of selenium which would be significantly higher than any dietary sele-
nium intake would be in Europe; so it is what we could call at the upper limit of a nutri-
tional benefit. The pharmacological effect of vitamins is much more likely than the
pharmacological effect of trace elements. As far as separating the effects of zinc from
the effects of vitamin A or both, I think your point is very well made that there will be
separate effects. There is an interaction of course between zinc and vitamin A metab-
olism: zinc is required for retinol-binding protein production and vitamin A carriage
around the body so the interaction between zinc and vitamin A metabolism is quite
clear. Many populations have combined zinc and vitamin A deficiency, whereas some-
times they have separate deficiencies and I think this has complicated interpretation
of results in trials in different parts of the world.

Dr. Steenhout: I would like you to comment on the fact that when we look for vita-
mins we know that food processing and food habits can change the intake. If I am look-
ing for a trace element like selenium there is a zone, as you reminded us, where the
level is low, as in Europe, and there is a zone where the level is higher. So it is not a
fast change, it has probably been like that since the origin of humanity because it
comes from the ground, there is some cycle. Why is the body and why is the evolution
of metabolism not better protected for some trace elements, for others protection
exists very well, but for some like zinc and selenium it remains very unstable if we are
not in the right range. Why is evolution not trying to protect us better? Secondly if we
look at selenium, if it is not in a deficient region in the US, there are some studies on
selenium supplementation in the frame of cancer prevention [3]. I didn't necessarily
see that the United States is a zone with a high selenium level and a lower level of can-
cer. Lastly a very funny question: what was the mood of the people in the Keshan
region?

Dr. Shenkin: I cannot comment on all of your questions, but I can certainly com-
ment on the last one. At the time it wasn't part of the studies, when looking at Keshan
disease. They were much more concerned about cardiomyopathy. Demonstrating that they could cure cardiomyopathy by giving selenium supplements was the way in which it was proved that selenium was important. Effects on mood are a new idea and they have to be confirmed. Your question about low intake is really interesting and I am not sure how to answer. There clearly are parts of the world where it is possible to live with a low-selenium intake. For example the New Zealand population is exposed to a very low-selenium intake and does not seem to be harmed to the same extent as the Chinese population. It may well be that it is necessary to be exposed not just to mineral deficiency but to some other stress at the same time. It is now recognized that Coxsackie virus infection is probably necessary to act as a further stimulus to cause cardiomyopathy to develop, whereas if you do not have that other stress then you do not develop the disease. I cannot comment on why the mechanisms to protect ourselves against zinc deficiency have not evolved better. As was suggested, perhaps the population generally has been able to move around and found a mixture of intakes which has made it possible to survive and grow. I can't recall what your third question was.

**Dr. Steenhout:** It was the difference of frequencies of cancer between zones with low selenium and high selenium.

**Dr. Shenkin:** There are some epidemiologic studies which have shown that in low selenium areas there are higher incidences of certain cancers. Especially in China, hepatocellular cancer is much more common in areas where selenium intake is low, and again providing selenium to these groups has been beneficial. But in other cancers the data are mixed, and it is not clear cut.

**Dr. Go:** I think you brought up a very key point, selenium. In the data that we have looked at from the cancer standpoint, there are a lot of compounding factors. In the Chinese studies, when you talk about the hepatoma situation, there is a hepatitis background, so there are some other compounding factors. This is why I have difficulty accepting one nutrient, selenium, as the cause of related or associated disorders, because there are some other factors in the environment that we need to look at. This is the reason why I said we may have to change the paradigm and we need to consider the environmental issue when we look at one single nutrient and a single mineral as causes of chronic disease.

**Dr. Rock:** I have to congratulate you for bringing up the point of the source of food and also in the study by Clark et al. [4] that you mentioned. It was actually done at 6 or 7 different clinical sites. A couple of them were communities with very low selenium in the soil, and the logical question would be, within those sites is a greater difference in terms of the risk for cancer seen? But the study was really not powered to ask that kind of question. Even though when you make paradigms and it looks very significant with prostate cancer, there were still only some 30 cases that developed over the period of time of the study. The other thing that happened in US, you mentioned the effect in Europe, but in the US we eat food from all over the world. Even though there are regions with lower selenium in the soil, it is now becoming more unusual to see differences in selenium status based on where you live because we are eating food from everywhere.

**Dr. Shenkin:** Just to mention a very important point. One interesting thing about the Clark [4] study was that when you look at the bottom tertile, the poorest status, in terms of plasma selenium, the upper limit of that group was a plasma concentration of 105 μg/l which is higher than most of us in Europe have got. So the status in United States is quite different from the status in Europe and this is why this trial must be repeated in Europe and in other parts of the world.

**Dr. James:** I would like to congratulate Dr. Shenkin on finally explaining why the Americans are optimistic and the European so miserable. I just thought that your sense of misery is perhaps a bit overdone in terms of the opportunity for work because
if you look at the two huge issues that are coming down, the calculations in the
European Union of the economic impact of osteoporosis are enormous. I just thought
that even the Europeans might eventually get into a NIH mode, given the current push
for a European Research Council, and cope with these big issues. The other one is
mental disease, and there is a huge issue now that if you look at the burden of ill health
then the capacity to function in older age is extraordinary. In selenium terms, Arthur
has been showing the quite important interactions of selenium, not only with thyroid
function but also with brain processing. I just thought that some of the more modern
techniques for looking at brain function might be amenable, particularly in Europe, if
we start off with the relatively deficient state to actually showing fairly short-term
effects of selenium on mood and all the other characteristics. I am quite intrigued that
you gave the impression that the world is still in disarray. Why are we not sort of get-
ting coherent on some of these big issues?

**Dr. Shenkin:** The difficulty I suppose is demonstrating a willingness on the part of
the major funders to support studies of this type. In the UK, our Medical Research
Council has been very poor at supporting any form of nutritional studies, especially
long-term nutritional studies because they are so expensive to perform and they have
to take place over a prolonged period. Although your point is correct about certain
forms of mood studies or cognitive function studies, where there may be some short-
term gains but most of these require long-term studies. One issue with osteoporosis is
that it is not a nutritional disease, it is an effect of hormone deficiency more than any-
thing, and nutritional intervention alone, although it is beneficial, by no means either
prevents or cures the disease, whereas we have other effective ways of manipulating
osteoblast and osteoclast function. The bigger story around osteoporosis is to ensure
that people have the appropriate drug treatment or hormone treatment and supple-
ment it with the appropriate levels of calcium and vitamin D to ensure that the bones
have got the substrates for optimal function.

**Dr. Go:** I fully agree with you, I share the viewpoint of Dr. James. There are long-
term studies. In Europe, the European Prospective Investigation into Cancer and
Nutrition (EPIC) project [5] involving 500,000 people in 10 countries, beautifully
designed studies, a lot of information coming out of this. The holistic approach is not
a single nutrient approach. They were looking at the totality of what people are eat-
ing and will hopefully be able to determine the role of diet in chronic disease preven-
tion. The same thing in the United States, the National Institutes of Health has the
Women's Health Initiative Project. The results of this study will be coming out in 2006.
In addition, the clinical trial for prostate cancer with selenium and vitamin E is ongo-
ing. The major problem, the challenge is basically we have to rely on people like
Dr. James whether the design is appropriate or not and how to design a long-term trial
for 10 or 5 years while the food supply is changing rapidly every year, that is the chal-
lenge we are faced with.

**Dr. James:** Can I come back on this question of osteoporosis not being nutritional.
For the 916 report we reviewed the whole of the calcium because there has been pre-
judice against the importance of calcium for decades, and I don't believe it has got
much of anything to do with osteoporosis. Given the fact that there is no relationship
to osteoporosis indexes and calcium intakes across the world, should we actually be
looking at the issue of bone and its maintenance in old age, for example in Asia rather
than in the United States or Europe, which have characteristically been on these weird
high-calcium intakes for years?

**Dr. Shenkin:** I am not sure I quite understand.

**Dr. James:** The data from the X-ray studies from across the globe were done about
20 years ago showing that actually there is an inverse relationship between indexes of
bone mass and indeed, if I remember correctly, the fracture rates and calcium intakes

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across the world. You touched on the mineral studies and intervention, I mean the evidence on calcium supplementation is really pretty wrong, isn't it, unless you go into these pharmacological doses.

Dr. Shenkin: I think the evidence is mixed. There are certain parts of the world where there is a relationship to calcium intake and the frequency of fractures, whereas there are other parts where there is not. That is part of the complication that the studies are variable. But I think it is impossible to build bone if you don’t have calcium intake. Part of the treatment and prevention is ensuring an adequate nutritional intake especially of calcium and vitamin D, but that is only one part of the story.

References
