Trace Elements: Contribution to the Efficacy of Nutritional Support

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Introduction

Efficacy of nutritional support can be defined in two main ways: the first relates to the production of new body tissue or the prevention of loss of existing tissue, this could either be growth in a child or repair or maintenance in an adult, and the second relates to how well the various body tissues are functioning. So the issue raised in the title of this chapter can be crystallized into ‘How do trace elements affect the amount and function of body tissues?’

Trace Elements and Substrate Utilization

For trace elements to have an effect on tissue mass, especially lean body mass, a link to nitrogen (N) balance and net protein synthesis, and to utilization of macronutrient substrates is required. Several lines of evidence support such a role, at least for selected trace elements, of which the best characterized is zinc.

In a classic paper, Rudman et al. [1] demonstrated that the key intracellular macro-elements, potassium, magnesium and phosphorus, are all required to be provided in total parenteral nutrition (TPN) if a patient is to utilize macronutrients and achieve positive N balance – omission of any one of these leads to negative N balance, even in the presence of adequate amino acids and energy.
Fig. 1. Relation of zinc balance to nitrogen balance and plasma insulin. From Wolman et al. [2].
It has generally proved to be difficult to demonstrate a similar degree of linkage between trace elements and N balance. However, in an elegant study on 24 patients requiring TPN, Wolman et al. [2] determined the effects of different amounts of intravenous zinc provision. The key observation was that most patients lost substantial amounts of zinc from the gastrointestinal tract, but that zinc balance could be achieved by supplying adequate amounts of intravenous zinc. A positive zinc balance was associated with improved nitrogen retention, and a better nitrogen balance (Fig. 1). Interestingly, plasma insulin was also found to increase, when a negative zinc balance was converted to a positive one. Adequate zinc provision is therefore necessary not only to stimulate protein synthesis, probably as a result of increasing the activity of the many zinc-dependent enzymes in the protein synthetic pathway, but also to stimulate an adequate insulin response and utilization of glucose as well as amino acids.

The essential role of zinc for protein synthesis in children has also been highlighted in a series of studies by Golden and Golden [3, 4]. In children recovering from malnutrition on a soya-based therapeutic diet, virtually all had an immediate increase in the rate of weight gain, when additional zinc supplementation was commenced. This was associated with increased nitrogen absorption and higher rates of protein turnover.

On the basis of such observations, Michael Golden [5] developed the concept of the type-I and type-II nutrient. Type-I nutrients are those, where the deficiency leads to a reduction in tissue concentration and a defect in a specific metabolic pathway, leading to loss of function and specific clinical signs of deficiency – most trace elements are in this category, e.g. iron, iodine, copper, selenium. A type-II nutrient is one, where a deficiency leads to a primary reduction or cessation of growth, but with little reduction in the tissue concentration of the nutrient – this group includes essential amino acids, and also minerals such as potassium, phosphorus, magnesium and sulfur – the one trace element in this group is zinc.

### Chromium and Glucose Metabolism

A further interesting interaction between a trace element and substrate utilization is the role of chromium in improving insulin action – this has been observed especially in non-insulin-dependent diabetes mellitus patients [6], but also in nondiabetic obese subjects with a family history of type-II diabetes mellitus [7], as well as during long-term TPN [8]. There is growing evidence for the value of added chromium in maintaining glucose tolerance, reducing body fat and increasing lean tissue mass [9], although some of the evidence is conflicting [10] and more studies are clearly required in this area.
Trace Elements and Efficacy

**Trace Elements and Tissue Function**

Trace elements inevitably affect the function of all body tissues, as a result of their widespread roles as enzyme cofactors in intermediary metabolism, in structural components of cells (e.g. zinc – fingers) and in protection of cells through the various antioxidant systems (e.g. zinc/copper superoxide dismutase, selenium in glutathione peroxidase). Often the precise mechanism of benefit of a trace element on a tissue is not known and hence this review will focus primarily on the actual benefits of trace elements in improving tissue function, rather than on the biochemical mode of action.

**Trace Elements and Immune Function**

Zinc plays a key role in most aspects of the immune system, and it is well recognized that zinc-deficient individuals have a greater susceptibility to a wide variety of pathogens [11]. However, not all aspects of immunity are equally affected by zinc deficiency, e.g. intracellular killing by macrophages is very sensitive and is rapidly restored by zinc supplementation, malaria or tuberculosis which depend on such macrophage killing may therefore be very sensitive to zinc deficiency. Similarly T-lymphocyte-dependent antibody responses have similar sensitivity. On the other hand, infections depending more on T-lymphocyte-macrophage interactions, or on T-lymphocyte-independent antibody responses are less sensitive to zinc deficiency. Some clinical studies demonstrating the benefit of zinc are summarized below.

Selenium supplements (200 µg/day for 8 weeks) have also been shown to improve lymphocyte proliferation, interleukin-2 receptor expression and cytotoxic and natural killer (NK) cell function in a group of healthy young adults [12]. This suggests that the immuno-enhancing effects of selenium in humans may require supplementation above the replete levels produced by a normal oral intake. This dose has also been found to stimulate immuno-competence in patients with head and neck cancer [13]. A key intervention trial with selenium performed in the USA showed that 200 µg selenium yeast, containing mostly L-selenomethionine, reduced the incidence of lung, prostate and colorectal cancer by nearly 50% in patients with previously diagnosed carcinoma of the skin [14]. This study is currently being repeated in European countries, where there is a lower habitual intake of selenium.

**Trace Elements and Susceptibility to Infection**

Although there is much in vitro evidence for the role of various trace elements and vitamins in immune function, the only way of demonstrating the clinical relevance of this is by conducting well-planned, prospective, placebo-controlled intervention studies. A number of these have now been performed.
in different patient groups and the results are summarized below. Only a few of these studies have specifically addressed the provision of an individual trace element, or combination of trace elements, most studies also providing selected or multivitamin supplements.

**Studies on Healthy Elderly Subjects**

The most striking evidence for an effect of a multivitamin/multitrace element supplement was obtained by Chandra [15]. In 96 independently living, healthy individuals, >65 years old, a wide range of nutritional deficiency states depletion was detected biochemically at the start of the study (e.g., for vitamin A 10%, vitamin C 20%, iron 13%, zinc 15%). A daily supplement providing approximately the recommended daily allowance for micronutrients, or placebo, was given for 1 year. The supplemented group not only improved in terms of micronutrient status, but they also had a significant reduction in the mean number of days of infection from 48 to 23 days, and mean number of days of antibiotic provision from 32 to 18 days, across the 1 year of study. This was found to be associated with improved indices of immune function, especially in terms of NK cell numbers, lymphocyte response to phytohemagglutinin, and the antibody response to influenza vaccine. This was a small study, and it was not possible to determine which of the components was most responsible for the benefit.

A further important study was in 725 institutionalized elderly patients (mean age 83.9 years) from 25 geriatric centers in France [16]. The effects of 2 years supplementation either with daily provision of the trace elements zinc plus selenium, vitamins (β-carotene, ascorbic acid, and vitamin E), trace elements plus vitamins, or placebo were studied. The proportion of patients remaining free of respiratory infection throughout the 2-year period was higher in the trace element group than in the other 3 groups, but in terms of the total number of all infections there was no significant difference between the groups. However, antibody response to influenza vaccine was significantly better at 28 and 90 days after vaccine in the groups receiving trace element supplements than in the other groups (Fig. 2). Similarly, the immune response at 270 days was also much better in the trace element group than in the group receiving vitamins. Intriguingly, vitamin supplements appeared to have a negative effect on the antibody response to influenza vaccine at 28, 90 and 270 days. This study urgently requires repetition, especially if zinc plus selenium is more effective on its own, than when combined with multivitamin supplements.

**Studies on Childhood Infections**

Zinc deficiency is prevalent in children in developing countries where diarrhea is also a major problem. A meta-analysis of 7 trials of zinc supplementation, 3 in children with acute diarrhea and 4 in children with persistent diarrhea, has recently been published [17]. Overall, in acute diarrhea trials,
Fig. 2. Seroprotected patients (%) after influenza vaccine. Results after 16 months in 140 elderly patients supplemented with placebo (P), trace elements (T), vitamins (V) or vitamins plus trace elements (VT) and vaccinated with H3N2 influenza virus. Seroprotection was defined as an antibody titre of 80 at the times shown after vaccination. From Girodon et al. [16].

zinc-supplemented children had a 15% lower probability of continuing diarrhea on a given day. In the persistent diarrhea trials, there was a 24% lower probability of continuing diarrhea, and a 42% lower rate of treatment failure in the zinc-supplemented children.

There are more limited data suggesting that the incidence of acute lower respiratory tract infection and clinical attacks of malaria may also be reduced by zinc supplementation [18].

A possible interaction between zinc and vitamin A status in terms of response to supplements has recently been explored by Rahman et al. [19]. In a study on 800 children (aged 12–35 months) in Bangladesh, a 2-week supplement of zinc, vitamin A, both, or placebo was given to children who were then followed for 6 months. Combined zinc and vitamin A synergistically reduced the prevalence of persistent diarrhea and dysentery. Interestingly, zinc alone was associated with a significant increase in acute lower respiratory infection, but this adverse effect was reduced by interaction between zinc and vitamin A.

Studies on the Critically Ill

There have been 3 important trials of trace element provision in critically ill patients. Firstly, in a trial of zinc supplementation in 68 closed head-injured patients [20], a group receiving additional zinc, intravenously and then orally, had significantly reduced mortality (12%) in comparison with a group receiving standard zinc supplements (26%). Moreover, the mean Glasgow coma scores
were significantly better on days 15–28. Unfortunately, the standard zinc group had more craniotomies for evacuation of haematoma, hence a bias may have been present.

In a placebo-controlled study of 20 severely burned patients, Berger et al. [21] provided intravenously for 8 days a supplement of zinc, copper and selenium, which had been designed to meet the losses of trace elements, the amounts of which having been measured in previous studies. Patients were studied for 30 days following injury. The only difference in immune function between the groups was a higher total leukocyte count in the trace element-supplemented group between days 10 and 20. However, this group had significantly fewer infectious episodes over the 30-day period than did the control group, mainly because of fewer pulmonary infections. This group also had a shorter hospital stay when the data were normalized for burn size.

Thirdly, a trial of selenium supplements alone has been performed in 42 intensive care patients with severe systemic inflammatory response [22]. Patients were randomized either to receive a standard selenium intake of 35 µg/day, or an intake of 530 µg for 3 days, followed by 285 µg for 3 days, then 150 µg for 3 days, and then the standard intake. The group receiving high-dose selenium supplements rapidly normalized plasma selenium concentrations, which were low in all patients at the start of the study. Of special importance was the observation that the requirement for hemodialysis was significantly lower in the extra-selenium group, and moreover the Apache III score decreased more in this group.

These 3 studies were all undertaken with fairly small numbers of patients, and the results need to be confirmed by other research groups. If proven to be generalizable, future studies will need to address the amount and duration of the trace element supplements.

**Selenium Deficiency and Virulence of Infection**

A further recent line of investigation relates to the observation that in selenium-deficient mice, a normally benign strain of the Coxsackie B3 virus mutates to a more virulent form, which can induce cardiomyopathy [23]. The viral RNA genome was found to have mutated in six regions when the virus was cultured at the end of the study. Recently the same group has demonstrated that influenza virus infection also induces a more serious lung pathology in selenium-deficient mice [24]. The mechanism of this in the influenza model is not yet clear, but may relate partly to increased oxidative stress as a result of low glutathione peroxidase activity, leading to increased NFκB expression and hence increased chemokine expression. Another explanation, not yet published, is that again there are multiple mutations in the viral genome leading to a more virulent virus being produced. This whole area requires further study, especially with regard to the relevance of these findings to man.
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Trace Elements and Muscle Function

The only trace element for which there is clear evidence for an effect on muscle function is selenium. Individuals who are selenium-deficient are at risk of developing skeletal [25] or cardiomyopathy [26]. Selenium supplements have frequently been shown to improve the symptoms of muscle pain and fatigue associated with these clinical syndromes. However, only a small proportion of all patients with severe selenium deficiency develop clinical signs and symptoms [27]. One trial has attempted to document systematically changes following repletion with selenium [28]. The only difference observed in the 10 patients when selenium deficiency was corrected was a significant increase in type-I skeletal muscle fibers, but with no change in muscle strength or electromyogram, and no effect on cardiac muscle. The precise reason why certain patients develop clinical symptoms when most do not is therefore still not known, although this may relate to the presence of a further stress, or viral infection. However, since these clinical deficiency states only occur where there is clear evidence of biochemical deficiency, provision of adequate selenium to prevent such deficiency is essential – it is unlikely, however, that muscle function can be optimized by minor alterations of selenium status.

Trace Elements and Bone Function

Although of less importance in the short-term, maintenance of bone health and function is essential in those receiving long-term nutritional support. There is only limited evidence for an independent effect of trace elements on bone health. There is a positive correlation between zinc intake and bone mineral density (BMD) in middle-aged pre-menopausal women [29]. A controlled trial of copper supplementation in middle-aged women showed no loss in BMD in the copper-supplemented group, compared to a significant decrease in BMD in the control group [30]. A small trial of calcium, zinc, manganese and copper supplements showed a positive effect on spinal BMD in post-menopausal women [31]. Bone function remains of concern in patients receiving long-term intravenous N, with many patients still developing a form of metabolic bone disease [32]. Aluminum and vitamin D have both been implicated in this, but the precise pathophysiology is still not understood.

Trace Elements and Cognitive Function

Of growing interest has been the possibility that aspects of cognitive function can be influenced by trace elements. In an early study, Benton and Cook [33] showed that the greater the amount of selenium in the diet, the greater the reduction in reports of anxiety, depression or tiredness following
Fig. 3. Influence of selenium content of diet on mood states. Effect of a high Se (226.5 µg/day) or low Se (32.5 µg/day) diet on Profile of Moods Score in 30 healthy young men. The ratio of the score at weeks 11–14 to the score at weeks 2–5 is shown. Redrawn from Finley and Penland [34].

5 weeks of selenium supplements. More recently, in a longer term study over 105 days, a high selenium diet of 226.5 µg daily was compared with a basal intake of 32.6 µg daily [34]. A high intake of selenium led to a significant improvement in several aspects of the Profile of Moods Score, especially in the ratio of clear-headed/confused, elated/depressed, composed/anxious, and confident/unsure (Fig. 3). Studies of this type may be important in helping to optimize the mood of a patient receiving nutritional support either in hospital or in the community.

How to Optimize Provision of Trace Elements

From the foregoing discussion, it is clear that optimization of intake in an individual patient is an imprecise science. Accurate measurement in a busy ward or intensive care unit of aspects such as net protein synthesis or tissue function is difficult if not impossible. In reaching a decision regarding the amount of provision for a particular patient, a number of factors can, and should be taken into account.

1) Sufficient trace element must be provided to prevent clinical deficiency states from occurring. This involves appropriate use of knowledge of
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requirements in health, modified by metabolic state and increased losses to assess the approximate on-going daily requirement. This can then be adjusted for the history of the patient in terms of the probable recent intake and estimated losses, to allow an estimate of the amount required for repletion and maintenance. Most of the commonly used enteral and parenteral products provide some excess of all the trace elements in relation to the normal daily requirements. Nonetheless, some additional supply may be needed, especially in patients with pre-existing substantial depletion, or large on-going losses.

2) Attempt to prevent a sub-clinical deficiency state by using intakes, which have been proved to have beneficial clinical effects in controlled clinical studies.

3) Measure the plasma concentration of zinc, copper, and selenium at the start of a period of nutritional support, and every 2–4 weeks thereafter, depending upon the type of nutrition used, and the clinical situation of the patient – interpret these results with an assessment of the acute phase response to determine if the trend of results is likely to be beneficial [35]. Red blood cell glutathione peroxidase may also be helpful in evaluating whole body selenium status.

4) Use a biochemical indicator of the efficacy of antioxidant systems – although not yet in widespread use, there is substantial evidence of increased production of markers of oxidative damage such as malondialdehyde in catabolic illness, and that these can be reduced by providing extra selenium and zinc [36]. Patients receiving home TPN also have increased excretion of such markers of oxidative damage, although this seems to be related more to the adequacy of vitamin E provision than to trace elements [37].

5) Since all trace elements are potentially toxic if given in excessive amounts, special care must be used, when providing such elements intravenously. There is some evidence of a possible harmful effect of excess chromium provision in children [38]. Recently, there has been substantial concern regarding excess provision of manganese leading to deposition in extra-pyramidal tracts in the brain and causing a parkinsonian-like condition [39]. Manganese status should be measured on patients receiving long-term TPN, the whole blood manganese concentration being a relatively convenient and accurate method of doing this.

Conclusion

Most of the work on trace elements in artificial nutrition is currently centered on zinc and selenium requirements, with some interest in chromium and copper. Iron provision remains of concern, but because of the substantial stores of iron, less effort is made to tailor iron supply on a daily basis. It is now
becoming widely appreciated that optimizing the supply of trace elements can significantly affect the outcome of an individual patient. Further prospective studies with varying amounts of trace elements in patients with a range of pathologies are required. These will provide the evidence necessary to ensure that trace elements will improve the efficacy of the rest of the nutritional support, which is being provided. It is, however, apparent that trace elements cannot be considered in isolation from the other micronutrients, and that there are substantial interactions, especially between trace elements and fat-soluble vitamins. Future studies therefore need to look at the totality of micronutrient provision, in relation to macronutrient supply and disease state.

References


Discussion

Dr. Grimble: In infected patients we see an increase in nitrogen output, which is a reflection of the upregulation of protein catabolism. We also see massive losses of trace elements through the urine. Is that an unfortunate effect of the infection, or is it an indication of upregulation of general mineral metabolism?

Dr. Shenkin: I think the evidence is that this reflects loss of protoplasm – it is a result of cell necrosis. As you catabolize intracellular protein, you also leak zinc, potassium, magnesium and so on, and these all come out in the urine. There are very close correlations between the amount of these losses and the amount of net protein catabolism. I don’t think it is anything more subtle than that, except that occasionally trace elements may form complexes with other factors that are being excreted, like ketone bodies or other organic acids, and these might increase the total losses in the urine.

Dr. Grimble: So it is not an attempt by the body to get rid of certain trace elements that might be a disadvantage to the individual during the inflammatory response.

Dr. Shenkin: I don’t think so. Clearly there are other things happening at the same time such that the body repartitions trace elements from the plasma, where they might be harmful in relation to infection and so on, but I believe the losses in the urine to be a spontaneous overflow following release from damaged cells.

Dr. Leverve: If you interpret the loss of micronutrients mainly as a result of necrosis, then you should expect an increase in plasma concentration, which is not usually the case. I’m not completely convinced that this is the sole mechanism explaining the micronutrient losses.

Dr. Shenkin: That’s a valid point. The whole range of trace element concentrations is seen in individuals who are extremely catabolic. One does see patients with high zinc concentrations early on as a response to severe catabolism, though it falls later as the zinc is cleared into the urine and into the liver. However, this depends on the timing in relation to the actual injury.

Dr. Leverve: Yes, but in most cases plasma zinc is low, but the urinary losses are increased.

Dr. Shenkin: The amount of zinc lost in the urine is very small. Although I have not worked out the exact plasma clearance, in relation to plasma concentrations the zinc lost in the urine per day represents a tiny proportion of the total zinc in the body.

Dr. Labadarios: You pointed out the danger of supplementing people during the acute phase response. Could you enlarge on that, because it is a relatively new concept that is emerging? Might we actually be doing harm with these supplements?

Dr. Shenkin: It depends very much on the patient group. If you are talking specifically about patients who are severely ill in intensive care, then I think we come back to a point, which has already been made, that part of the acute phase response is designed to partition trace elements in a particular way. The classic example is the dramatic effect on iron. Serum iron falls precipitously following surgery and will
stay low for weeks after elective surgery. The iron has been taken away from the plasma and captured by lactoferrin and especially by ferritin in the liver. There are very good examples, where iron supplementation in various patient populations has exacerbated infection or caused recrudescence of quiescent infection. There is not such clear-cut evidence about zinc supplementation in that situation. There was one study that showed that with very high zinc intakes fever was increased in a population of infected patients randomized to low-zinc or high-zinc intakes [1]. Fever increased with a high zinc intake, but is a high fever necessarily a bad thing? There was no other obvious detriment to giving a high-zinc intake. Zinc does seem to do something during the acute phase response, because it falls in plasma and is repackaged into the liver. It probably enhances acute phase protein synthesis after being trapped by metallothionein. I think everybody recognizes that the trace element requirement is a bell-shaped curve. You get deficiencies on one side, toxicity on the other side, and beneficial effects in the middle. For some micronutrients, like selenium, the bell is very narrow; for others, like zinc, it is a bit wider; while for others it may be wider still, but how wide it is in the acutely ill patients we don’t know at present.

Dr. Calder: You highlighted studies that showed significant beneficial effects of zinc on infectious outcomes, but pointed out some contradictory observations. I wonder whether these contradictory results reflect the type of infection, the age of the individual, or any underlying borderline deficiencies of other nutrients that might be exacerbated by the provision of zinc.

Dr. Shenkin: That is a very important point. Some of the most convincing studies have been in the elderly, where the immune system has of course deteriorated with age. In that situation, anything you could do to stimulate the immune system and allow recovery from an infectious challenge is presumably a good thing. The trouble with all of the studies is that it has not been possible to demonstrate that the people who have done best have been the ones who have been the most deficient. You can start with a population with a certain nutritional status and deficiencies of all sorts of nutrients – zinc, selenium, folic acid, iron, vitamin C, and so on. Most people in institutions are multideficient. You then supplement them with a variety of things and the population as a whole may well do better, but which people in the population have done better? And why have they done better? For reasons, which I have never fully understood, the people who have performed these studies haven’t given that information in their papers, maybe because they didn’t make the right measurements or because the data were contradictory. It would be really helpful to have more carefully characterized populations to determine who are the individuals who benefit.

Dr. Haschke: You didn’t mention iron very much during your talk, but it has now surfaced in the discussion. I think iron is extremely important and requires more indepth discussion. It is a trace element that is usually given in excess during situations involving blood transfusions, or when there are burns, or where there is hemolysis. As you mentioned, iron is immediately removed from the bloodstream by the body during any stress situation, for obvious reasons. Iron is a pro-oxidant and certain bacteria need it for growth, so there are good reasons for removing it from the circulation. You also mentioned that too much iron in the wrong place in the body is probably a negative factor for health and is associated with an increased frequency of infections or complications. We don’t have to repeat Golden’s study from the 1970s, looking at the body iron content of children in Jamaica who died from malnutrition. Those who had the highest body iron content had the worst prognosis. What is your view about this? How dangerous is iron, and do we have to intervene if we think that there is too much iron around in an acute situation?

Dr. Shenkin: That’s a difficult question and I don’t think there are any data. I know there have been studies in intensive care about the early provision of blood transfusion
which have demonstrated a poorer outcome with large transfusions, but I am not aware of any attempts to either assess total body iron in this group of patients or try to reduce it. If the iron is stored away in ferritin and hemosiderin it is probably safe, and I suspect that it is only when the iron has been released, as with increased hemolysis, that there is likely to be a problem.

**Dr. Carpentier:** How adequate is the plasma ferritin level as an indicator of iron stores?

**Dr. Shenkin:** It depends on the patient population. In this particular group of individuals – who are critically ill, burned, septic, or what have you – the ferritin is an acute phase protein and you get high ferritin purely as a response to the infection or trauma. Thus, though ferritin is a good marker of iron stores in elderly people in a nursing home for example, it does not really help you in this group of acutely ill patients.

**Dr. Labadarios:** Just for information, the recent WHO recommendations for the treatment of severe malnutrition actually prohibit iron supplementation in the first 2 weeks of nutritional rehabilitation [3]. After 2 weeks it can be given safely. The reason that it should not be given in the first 2 weeks is because of the immediate danger of oxidative damage, which is known to be associated with increased morbidity and mortality.

**Dr. Leverve:** You showed us data suggesting that trace elements improve the vaccination response in the elderly people, and the response was different when you combine trace elements and vitamins. What is the reason for that?

**Dr. Shenkin:** I was hoping somebody in the audience would tell me. It is extraordinary! Part of the difficulty here may be that we are putting too much emphasis on antioxidants and on the antioxidant effects of these nutrients. What I was trying to point out is that trace elements have effects other than their antioxidant effects – effects on controlling metabolism for example – and it may be that the combination of certain trace elements and antioxidant vitamins somehow interferes with the benefits of the antioxidants. For example, it could mask the beneficial effects of zinc on protein metabolism. There are no data to help us to interpret this finding and the study seemed large enough, as it involved 725 people. It is extremely difficult to pin down what was happening, except to say that zinc and selenium have different actions, and they were not acting through their antioxidant effects, but through some other mechanism.

**Dr. Calder:** There is one study of vitamin E that is perhaps relevant to this discussion. It was a study published by Meydani et al. [2] in JAMA in 1997, where they gave elderly subjects increasing doses of vitamin E and found that T-cell-mediated delayed-type hypersensitivity increased with increasing doses of vitamin E, whereas the antibody response to vaccination increased at a low dose and then declined at a high dose. This suggests that, while vitamin E enhances T-cell function to some extent, once a particular dose of vitamin E is achieved then B-cell responses decline. The implication is that vitamin E causes an imbalance in different aspects of immune function when you get to a particular dose.

**Dr. Segal:** On a population level – particularly in relation to subclinical deficiencies in developing populations – one of the confounding factors is the nutrient content of staple foods. In South Africa, where the staple is maize, the selenium content of locally grown maize is adequate, but when maize is imported the selenium content is low. So what should be the approach at a population level when it comes to trace elements, and selenium in particular? Should we be supplementing foods? There are people who are very much opposed to supplementation on both theoretical and philosophical grounds.

**Dr. Shenkin:** There are parts of the world where supplementation has been used, notably Finland. It appears that the addition of selenium to the fertilizers used to
encourage crop growth in Finland may have accounted for some of the benefits that the Finns have seen over the years in relation to heart disease, and possibly also to certain forms of cancer. But there is, as you say, a major public health debate about this. We are going through that now in the United Kingdom. We know that selenium intake in the UK has fallen by almost 50% over the last 30 years, because we are growing our own wheat in soil which is low in selenium, whereas previously we imported wheat from America with a high selenium content. There are people who are passionately against interfering with the food supply, on the grounds that supplementation could be harmful. However, there are examples where supplementation can work, so maybe it is worth trying it on a controlled basis in selected areas, to see if any benefit can be shown.

_Dr. Okada:_ You stressed the importance of zinc and selenium. My understanding is that there are different clinical manifestations of deficiency of these nutrients. For example, total parenteral nutrition (TPN)-induced zinc deficiency causes skin lesions and abdominal symptoms, while dietary deficiency causes growth retardation. The same is true for selenium – in some cases there is cardiac arrest or cardiomyopathy, in others there may be painful symptoms in the lower legs. What is the cause of these differences?

_Do. Shenkin:_ It is difficult to explain, though there is comparability between the dietary selenium deficiency seen in Keshan disease in China and the cardiomyopathies that are seen during TPN. However, I don't think the skeletal muscle myopathy and some of the nail changes that are seen in TPN have been described in the Chinese population or in New Zealand, where dietary selenium deficiency also occurs. The symptoms of selenium deficiency with TPN may have something to do with the speed with which it occurs, whereas dietary deficiencies tend to be more chronic.

_Do. Meguid:_ I was fascinated by your data on cognitive function and trace elements. I know you had limited time, but do you have any other data concerning thiamine in nursing homes or intensive care unit (ICU) settings, where there are confused patients?

_Do. Shenkin:_ There is quite a lot of data on thiamine. Thiamine in the ICU is an exceptionally important micronutrient, not just from the point of view of cognitive function. There are many case reports now of acute thiamine deficiency complicated by cardiac failure and acute lactic acidosis in the ICU setting, though not so much on the cognitive aspects. However, I assume it is much more difficult to study cognition in these acutely ill patients. Nevertheless, there is a considerable amount of data on thiamine in elderly individuals in nursing homes suggesting that supplementation can be beneficial. Unfortunately, many of these studies have not looked only at thiamine but at multivitamin supplements, so it is difficult to pin the effects down to one vitamin.

_Do. Griffiths:_ Thiamin might of course have a direct effect, but there is the potential for minerals to have indirect effects on cognitive function as well. You showed the marked influence they have on the immune system, and we know about the effects on mood and elation that occur with chronic inflammation, related to a range of different cytokine signals. So there is a possibility of an effect on mood and elation that is independent of any direct effect of the minerals.

_Do. Labadarios:_ When you talk about the micronutrients, you have a difficult task in defining end points. An example of this is the emergence of a role for micronutrients in cognition and mood. I recently reviewed a study of the effects on ‘mood’ – in a general sense – of a multivitamin, multimineral supplement given in rather high dosage. The study was placebo-controlled and well designed [4]. The investigators selected highly stressed subjects and determined the effect of the supplement on their mood. Both the placebo group and the active group responded, but the active group responded significantly much better. The outcome could be a claim that you might use these
particular supplements to control mood. How does one respond to studies like these? For a start, how do you define mood? That’s an impossible task. And then we are required to accept results that we don’t understand, even though we do know that many micronutrients are involved in brain function.

**Dr. Shenkin:** This new area is just taking off. It is fascinating to watch the development of a whole new science – psychoneuroimmunology. There are many factors that can influence the interaction between the brain, the nervous system, stress, and the immune system, and nutrition is just one of them.

**Dr. Barclay:** In ICU patients, how important is the role of the gut in trace element nutrition? Is it better to give trace elements enterally or parenterally during the acute phase, and are there differences between the trace elements?

**Dr. Shenkin:** All the studies I know of have looked at intravenous supply. As far as I’m aware there have been no well-controlled studies of enteral supply. Most of the earlier studies took place at a time when the majority of patients were on almost complete TPN; now that more patients are receiving enteral nutrition, it makes sense to give trace elements via the gut, because, as with all the other nutrients, the gut acts as a regulator. Personally I am more comfortable with giving trace elements by the gut, allowing the gut to decide whether it wants them or not, but this depends on adequate gut function.

**Dr. Chioléro:** If you want to have a rapid effect in acutely ill patients – and we have a lot of experience of this in Lausanne – it is probably best to give them by the intravenous route; you will have a better effect. Under these acute circumstances, trace element absorption from the gut is not very good.

**References**