Metabolism and Metabolic Effects of Trace Elements

Walter Mertz

Beltsville Human Nutrition Research Center, Agricultural Research Service, Department of Agriculture, Beltsville, Maryland 20705

Modern trace element research is concerned at present with 17 elements, the essentiality of which has either been established or is suspected. Even when we concentrate on the seven or eight elements for which problems of deficiency or excessive exposure are known to occur in man, the multitude of their individual metabolic pathways, requirements, and interactions with the environment represents a very large compilation of data that is essential for understanding the nutritional situation but extremely difficult to comprehend. The following discussion attempts to classify the most important aspects of the trace elements' metabolic behavior and interactions into a few categories that might serve to simplify the complex picture by offering for discussion a few principles that are believed to govern trace element metabolism.

The second part of this discussion addresses the effects of trace elements on the metabolism of nutrients in the organism. Subtle metabolic derangements are often the predominant expression of the marginal trace element deficiencies which are the major problems in developed societies. Their relevance to health is often controversial, in contrast to the appearance of clinical consequences of more severe deficiencies. Some principles which might be helpful in evaluating the health relevance of the many metabolic signs of marginal trace element deficiencies are proposed.

METABOLISM OF TRACE ELEMENTS

Absorption

Cell membrane physiologists and biochemists have long recognized that the mechanisms of membrane transport depend on the chemical nature of the substrate. For example, gases, small neutral molecules, and small anions can easily diffuse across membranes, whereas larger anionic and most cationic species require a specific transport mechanism, e.g., facilitated diffusion or active transport. This principle can be applied to the intestinal absorption of trace elements in general terms (Table 1). The absorption of elements that occur in the form of small anions
TABLE 1. Environmental versus nutritional influences on trace element status

<table>
<thead>
<tr>
<th>Category</th>
<th>Elements</th>
<th>Major influence</th>
<th>Range of tissue concentrations</th>
<th>Absorption efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anionic</td>
<td>F, I, Se, Mo, Cr(VI)</td>
<td>Environment: imbalances defined by areas, regions</td>
<td>Large</td>
<td>High</td>
</tr>
<tr>
<td>Cationic</td>
<td>Na, K, Mg, Ca, Cr(III), Mn, Fe, Cu, Zn</td>
<td>Dietary form of element: interactions, availability</td>
<td>Small</td>
<td>Low</td>
</tr>
</tbody>
</table>

in foods (or are converted into small anions in the digestive tract) is greater than that of cationic forms and often nearly complete. Such forms are usually less subject to dietary interactions and to homeostatic control at the level of intestinal absorption. Therefore the level of environmental exposure to these elements is an important, perhaps the most important, determinant of the nutritional status of populations living in that environment. This proposition is supported by the following examples: All elements that occur in forms of small anions present geographically or locally circumscribed problems of under- or overexposure. Deficiency and toxicity of fluorine and iodine can be defined by exact geographic descriptions: Iodine deficiency (1) is delineated worldwide by regions of various size, ranging from very small areas (e.g., parts of Switzerland) to parts of whole continents (e.g., the “goiter belt” in the United States). The fluoride environment, on the other hand, often can be defined by localities (1), especially when manmade changes by fluoridation of drinking water have occurred. Selenium deficiencies and excesses are also closely related to the geochemical environment (2); large regions worldwide are low in selenium, but natural environments with near-toxic concentrations of selenium also have been described in China (3).

Among the transition elements of known importance in human nutrition, molybdenum occurs predominantly in anionic form because of its preferred high oxidation state. Molybdenum deficiency is recognized as a major regional impediment to plant crop production (4), whereas excesses induce severe animal diseases in circumscribed areas because of their interference with copper metabolism (5). Both excesses and deficiencies of molybdenum are tentatively implied as risks for a variety of diseases in humans, e.g., deficiency as a risk factor for esophageal cancer in areas of China and South Africa (6), and toxicity as a contributing factor for a new syndrome of genu valgum in one area of India (7). The compounds of the hexavalent oxidation state of chromium are also anionic. Being exclusively manmade and arising from industrial activities, they are much better absorbed than the natural, trivalent form and have created an increased risk for lung cancer, strictly localized within certain chromate plants. The “new trace element” vanadium also prefers a high oxidation state and should be considered among the small anions.
However, our knowledge of the role of that element in human nutrition is inadequate as a basis for further discussion.

The facts presented here lead to the following tentative conclusions:

1. Our main concern for this group of anionic elements is with the influence of the environment on nutritional status.
2. Because of inefficient mechanisms regulating absorption, we are concerned about the risk of overexposure.
3. The dietary requirement for these elements can be expected to be very close to the absolute requirement, the amount that must be absorbed by the organism. This has important implications for the design of intravenous nutrient solutions.
4. This category of elements is not subject to as profound dietary interactions affecting bioavailability as that of the cationic group; this is an important advantage in relation to large-scale intervention by individual supplements or enrichment.

The nutritionally important cationic elements, in contrast to the first category, are subject to strict homeostatic regulation of their metabolism, in some cases via hormonal control, either at the absorption or excretion level. They comprise the alkaline metals lithium, sodium, and potassium, the earth alkali elements magnesium and calcium, and the transition elements with the exception of molybdenum. Whereas the alkali ions are readily absorbed and their levels regulated by control of excretion, all remaining cationic forms have a very strong intestinal regulatory component. That component determines the efficiency of intestinal absorption from dietary sources according to the nutritional need of the organism, provided the elements are present in an absorbable form. The latter qualification has enormous nutritional implications: Transition elements, unprotected by organic ligands, are insoluble at the pH of the intestinal milieu. Thus the chemical state of the cationic elements in the intestines is the second predominant factor influencing absorption and, in many cases, overriding the homeostatic control of the organism. For example, even in severe iron deficiency, the organism cannot increase absorption efficiency enough to meet its requirements if the dietary iron is not in an available form. Bioavailability is dependent on the chemical form in which the cationic element is present in the food, as well as on innumerable dietary interactions in the gastrointestinal tract with other food components that can displace the original ligands and strongly influence bioavailability. With the exception of the alkaline metals, the cationic elements of nutritional importance are less than completely absorbed, with efficiencies ranging from less than 1% (chromium) (8) to more than half of the amount present (zinc) (9). The differences of absorption efficiencies are almost as impressive for individual chemical compounds of one element: The absorption of iron in one and the same individual can range from less than 1% (certain nonheme forms) to more than 25% (heme iron) (10). These considerations strongly emphasize the importance of chemical form and interactions on nutritional status for the cationic elements. They also suggest manipulations of bioavailability and dietary interactions as a more effective means than fortification alone for improving nutritional status of population groups. A three-fold increase of available
iron can be readily accomplished by such measures, whereas a three-fold increase of the total amount of iron in the diet by fortification would be very difficult, perhaps impossible, to accomplish. Many interactions are at least qualitatively known; some are discussed elsewhere in this book (O’Dell, this volume).

We can propose the following principles to delineate the nutritional implications of the cationic elements: (a) Because of low absorption efficiency and strong extraneous influences on biological availability, nutritional problems almost always arise from dietary interactions; the absolute amount in most diets would be sufficient to meet requirements if it were available. (b) Because of these dietary interactions, the cationic elements are almost always better absorbed when given separately than they are as part of a meal. (c) The influence of the geochemical environment is of relatively minor importance compared to that of dietary interactions. (d) Because the spread between absolute requirement and dietary requirement for these elements is very large, the amounts administered as part of intravenous nutrition have to be carefully calculated. (e) Nutritional problems of the cationic elements (excluding the alkali and earth alkali metals) are predominantly, perhaps exclusively, problems of biological availability.

Intermediary Metabolism of Trace Elements

Once absorbed, all trace element compounds, whether cationic or anionic, must undergo a chemical transformation before they can exert their biological function. This may involve a change of the coordination sphere or oxidation state, but in all cases it results in specific binding to transport substances that direct the elements to their target organs and the synthesis of the elements into the chemical environment of their site of action. In general, these transformations are not limiting, except for special circumstances: Severe derangement of energy metabolism and interactions within the organism with excesses of competing elements can impair these processes. It has been postulated that the reaction of copper with thiomolybdate results in a complex that cannot be easily utilized. The antagonism of cadmium and mercury against selenium is believed to result from a similar mechanism. In addition, two elements present special problems: The essential trace element cobalt cannot be transformed by the animal organism into the form that can be built into the target molecule; thus the cobalt requirement of animals can be met only by preformed vitamin $\text{B}_{12}$, which is synthesized by ruminant bacteria and certain fungi. The situation for chromium is more complicated. For its interaction with insulin, chromium must be transformed into a dinicotinic acid–glutathione chromium II complex, termed glucose tolerance factor (11). There is as yet no clear evidence about whether the capability of the human organism to transform inorganic chromium into the active form is limiting, but an inbred mouse strain (the genetically obese diabetic mouse) is apparently unable to perform this transformation, as it responds only to glucose tolerance factor chromium, not to simple compounds (12). The chemical transformation of trace elements in the organism offers some interesting nutritional implications: (a) Many transformations are energy-dependent
reactions, and all involve organic substances in the organism that must be synthesized and regulated. Thus although these reactions are not limiting in an organism of good nutritional status and functioning metabolism, they can become severely limited by nutritional imbalances that impair the general metabolism (e.g., protein deficiency or excessive intakes of competing elements). (b) A better understanding of the transformations of individual elements in the organism and their physiological significance holds substantial promise for the development of methods to diagnose the trace element status of individuals. Most researchers agree that determination of the total concentration of an element in body tissues or fluids provides very limited information concerning that part of the total which is functionally important and related to nutritional status. The important role of renal excretion mechanisms in homeostasis cannot be assessed and quantified unless the proportion of ultrafilterable forms of a trace element among the total is known. It has been suggested that moderate decreases in the total concentration of an element in serum may reflect marked reductions of one small but biologically meaningful species. The analysis of such fractions, which appears to be technically feasible with modern instrumentation, is one of the high priorities of trace element research (13).

**Homeostatic Regulation**

The tendency of higher organisms to maintain their "milieu interne" strongly interacts with the environment and strongly affects nutritional needs and status. Homeostasis, as applied to trace element nutrition, can be interpreted as the tendency to maintain adequate concentrations of trace elements at the physiologically most important sites of action, followed by those sites that are less important for immediate survival and subsequently by physiologically important body stores. Thus concentrations in the vitally important structures are kept remarkably constant, even in moderate deficiencies, when other, less vital sites of action become depleted. Preceding that stage the saturation of specific transport proteins may decrease as the only sign of a suboptimal intake, and this desaturation in turn follows an exhaustion of specific tissue storage pools. Conversely, storage pools are the first defense against overexposure, followed by transport proteins and enzymes of increasing importance for the vital processes. These defense mechanisms become effective after the regulatory capacity of absorption and excretion mechanisms has been exhausted. Thus we can construct a hierarchy of sites which are involved in homeostatic regulation or dependent on it. Such hierarchy can be established for iron and to some degree for zinc; it gives important directions for the choice of substrates to determine nutritional status.

Two examples serve to illustrate extreme conditions. The zinc enzyme carbonic anhydrase is absolutely vital for life; no changes would be expected with any degree of zinc deficiency. On the other hand, the mildest stages of iron deficiency can be diagnosed by analysis of the iron storage pool (the size of this pool is reflected in the concentration of serum ferritin), by the saturation of the specific iron transport protein transferrin, or by the measurement of absorption efficiency of a test dose of the element.
In addition to these specific mechanisms of regulation of the milieu interne, the kinetics of total body loss of trace elements by themselves present a powerful mechanism of homeostatic control. The loss of most trace elements from the organism, as measured by radioactive or stable isotopes, is best expressed by a series of first-order reactions: The loss is a constant fraction of available stores at any given time. Although excretion kinetics containing three or more components are common and the equations describing them may be very complex, an overall fractional excretion rate can be estimated, especially when the daily dietary intake of that element is reasonably constant. The constant fractional excretion has strong implications for homeostasis in that the absolute amount of a trace element lost per day is much greater when the body stores are high than it is when they are low. Thus the absolute as well as the dietary requirement to maintain the existing status varies with the size of the trace element pool. This fact has great significance for the assessment of nutritional status. Balance studies are widely used to determine nutrient requirements based on the apparently simple logic that a daily intake less than the daily loss must result in deficiency. This conclusion is not completely correct, because even with a lower intake a new equilibrium will be established as soon as the body stores have declined to a point where the fractional excretion rate equals the intake. The results of balance studies thus indicate the amount of a nutrient required to maintain the existing state of tissue stores but not the true requirement. The controversies that have arisen from purported requirements as determined by balance studies in different countries are easily reconciled when this definition of balance is applied (14).

These considerations emphasize the importance of the “time factor” in trace element nutrition. The time factor expresses the buffering effect of homeostatic regulation on short-term changes of dietary intake (or of bioavailability that might affect the amount actually available to the organism). Even strong effects of acute experimental interventions cannot be extrapolated to suggest permanent influences on nutritional status, because homeostatic regulation with time might well be able to compensate for the observed acute effects and prevent an impact on nutritional status. This was convincingly demonstrated by two independent groups of investigators who studied the acute and long-term effects of two dietary interactions on iron bioavailability. In spite of a strong, immediate stimulation of iron absorption by vitamin C administration and of strong depression by isolated soy proteins, none of the treatments administered over extended periods of time were found to have any noticeable impact on iron status of the subjects (15,16).

Consideration of the “time factor” is equally important for the design and interpretation of balance studies. It is only a matter of time for the test subject who is fed any intake above the minimum requirement to reach balance. When the intake during the study is below the subject’s habitual intake, the time to reach balance will depend on the turnover rate of the body pool of that element. When, on the other hand, the experimental intake is above habitual amount, the time required will be a function of the rate at which the body pool is increased by the excess intake. Even when balance is obtained, conclusions as to the requirement cannot
Nutritional Implications of Homeostasis

1. Homeostatic regulation of trace element levels at the functional sites is indispensable for maintenance of life under all but ideal, protected conditions.

2. Homeostatic regulation is the scientific basis for the acceptance of "ranges of safe and adequate intakes" recommended in some countries, rather than the recommendation for one single intake level.

3. The concept of homeostatic regulation applied to trace element balance studies questions their validity as sole criteria for the establishing of requirements.

4. The concept indicates the importance of the "time factor" in the design and interpretation of any intervention on nutritional status.

EFFECTS OF TRACE ELEMENTS ON METABOLISM

Alterations of metabolism are the events underlying all clinical signs of trace element deficiency or toxicity. It is logical to assume that they precede the appearance of structural or functional disturbances, and that they may be the only recognizable indicators of a suboptimal trace element status for certain periods of time. The duration of those periods decrease with decreasing adequacy of the trace element intake. Marginal deficiencies, the major concern of trace element nutrition in developed countries, can lack clinical signs altogether, raising the question of the importance for health of the metabolic changes observed. Although there is general agreement that the occurrence of clinical signs of a trace element deficiency should be cause for intervention, there is no such agreement for metabolic changes as compelling reasons for intervention. The problem is complicated by the multitude of metabolic changes due to trace element imbalances, but it is possible to delineate a sequence of events which, except for the timing, is applicable to the development of all trace element deficiencies (Fig. 1). We can distinguish four stages in the development of deficiency.

1. The first consequence of inadequate intake of a trace element consists of changes in the metabolism of the trace element itself, as was previously discussed. Homeostatic mechanisms result in increased absorption efficiency or conservation through control of excretion. This stage may be accompanied or followed by slow exhaustion of body reserves of the element and by a diminishing degree of saturation of the specific carriers of blood. This stage indicates increased risk for deficiency but does not constitute deficiency by itself. It could be designated "initial depletion phase."
<table>
<thead>
<tr>
<th>STAGE</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Initial depletion</td>
<td>Restricted to changes of metabolism of the element itself (adjustment of absorption, excretion; desaturation of carriers)</td>
</tr>
<tr>
<td>II. Compensated metabolic phase</td>
<td>Changes of element-dependent functions, compensated by independent systems unless stress is imposed</td>
</tr>
<tr>
<td>III. Metabolic deficiency</td>
<td>Changes of major metabolic pathways, nucleic acids, protein, carbohydrate, fat</td>
</tr>
<tr>
<td>IV. Clinical deficiency</td>
<td>Clinical signs, disease, death</td>
</tr>
</tbody>
</table>

**FIG. 1.** Stages of trace element deficiency. This represents a general scheme, to be adjusted when applied to individual elements.

2. The next stage is characterized by an impairment of specific, trace-element-dependent biochemical functions but without any measurable changes in the level and metabolism of substrates influenced by these functions. For example, the low glutathione peroxidase activity in New Zealanders living in a low-seelenium environment does not result in noticeable oxidative damage, probably because of compensation by glutathione transferases and other functions that are independent of selenium. During the initial phase of chromium deficiency, the mild degree of insulin resistance is compensated by increased insulin production and does not lead to glucose intolerance. The reduced degree of lymphocyte transformation observed in mildly iron-deficient subjects has little consequence for healthy people, possibly because of other compensating mechanisms. This “compensated phase of deficiency,” although not constituting a health risk per se, is clearly associated with increased risks, whenever organisms at that state are exposed to metabolic or environmental stress. Compensated selenium deficiency can become uncompensated by simultaneous vitamin E deficiency or by nutrients that impose oxidative stress, chromium deficiency by high glucose intakes, iron deficiency by hemorrhage.

3. The third stage is the uncompensated form of deficiency, characterized by noticeable changes of the trace-element-dependent metabolic substrates in the organism. The great number of known metabolic disturbances in different trace element deficiencies can be considered from two perspectives: (a) in relation to the risk for the final, severe stage of clinical deficiency that the third phase predicts; and (b) with regard to risks for apparently unrelated diseases that the metabolic disturbance may create. For example, the metabolic consequences of chromium
deficiency, elevated circulating insulin concentrations and glucose intolerance, are recognized as independent risk factors for cardiovascular disease. Selenium deficiency at these stages is accepted by many as a risk factor for cancer at certain sites, and copper deficiency is suspected as a risk factor for many aspects of cardiovascular disease.

4. The last phase is characterized by worsening of the metabolic derangements and by the appearance of structural and functional lesions, resulting in serious disease.

The degree of knowledge of the sequence of events leading from inadequate intake to the final, clinical phase of deficiency varies from one element to the other. It is substantial for two trace elements, iron and iodine, and is limited to a description of very general phenomena (e.g., impairment of growth, reproduction) for the "new trace elements." The study of the metabolic derangements arising from marginal trace element deficiency is promising for understanding the mode of action of the essential elements; it offers the potential for establishing diagnostic procedures sensitive enough to detect marginal deficiency; and finally, it raises important questions of public health policy. Understanding of the function of zinc, for example, long recognized as essential for human growth and development, was decisively increased by the discovery of the element’s essential role in enzymes that regulate gene expression (17). On the opposite end, the interesting observation of a high incidence of sudden cardiac death in arsenic-deficient animals is at present unexplained by metabolic events (18).

The determination of metabolic changes, even if those may not be specific by themselves, can serve to reinforce the results of elemental analysis in body fluids and thus strengthen the reliability of the diagnosis of marginal deficiency. For example, the diagnosis of chromium deficiency on the basis of chromium analysis in serum and urine is tentative at most; it is reinforced by the demonstration of glucose intolerance in the presence of adequate insulin concentrations.

The implications of metabolic consequences of trace element deficiencies for public health policies are controversial. The controversy is of little importance in areas where a trace element deficiency results in a sizable number of clinical cases because the latter should provide sufficient motivation for nutritional intervention. It becomes very important, however, in situations where clinical cases are lacking, as in the "compensated metabolic phase" of deficiency and where extensive supplementation programs would be necessary to correct the marginally inadequate intake. No health risks have been identified from the low selenium intake of the population in areas of New Zealand despite low levels of the selenium enzyme glutathione peroxidase (2). In some areas the compensated metabolic phase of iodine deficiency is considered inconsequential (19), and the general deterioration of glucose tolerance with increasing age (20), which is at least in part related to marginal chromium deficiency, is considered by many a natural aging phenomenon. At the extreme end, mild degrees of iron deficiency are believed by some to confer benefits rather than risks for health (21). These controversies are illustrated by the
often astounding differences of national or international recommendations for trace element intake (14). A resolution may be expected from additional research: The convincing demonstration that even the "compensated metabolic phase" of trace element deficiencies constitutes a risk factor for seemingly unrelated diseases, including infections, cardiovascular disease, cancer, disturbances of physical and mental development, etc., may resolve the controversy. This evidence, however, is not yet strong enough. There remains the fact that the occurrence of marginal deficiencies (phases 1 to 3) indicates increased risk for serious disease of phase 4 in the unknown proportion of the population that may have extreme dietary requirements or unusual dietary habits, or is exposed to permanent, substantial stress. Depending on local circumstances and the background of the decision-makers, such a risk may be considered unavoidable for the adult population, but it should never be accepted for pregnant women or for infants and children.

REFERENCES

DISCUSSION

**Dr. Thompson:** Do you think it is necessary to have depletion before you become deficient? I am thinking, for instance, of small babies; we wondered whether they might have the right concentration of zinc but be small, and then require more zinc to grow. Perhaps that is what happened in Dr. Aggett’s pigs, with the tissues not being depleted even though the pigs had a zinc-deficient rash.

**Dr. Mertz:** There can be no clinical deficiency unless specific sites are depleted. If you are referring to depletion of total body zinc, there may not necessarily be depletion, but when it comes to the active, specific sites, they must be depleted.

**Dr. Thompson:** Do you think it is possible that in growing animals you limit only its growth? It just does not grow and not eat, waiting for the available zinc to increase and then it grows. The whole body content or concentration may remain normal until the animal starts to grow again.

**Dr. Mertz:** If the plant stops growing it is because the specific nutrient required for growth is not adequate at the specific site. There may be plenty of the nutrient in an unavailable form at other sites, so you cannot measure a significant decline of concentration in the whole plant. The question in the human organism is, of course, whether a deficiency stops growth, to be resumed later, or there are additional, irreversible consequences. Much of the evidence supports the latter alternative.

**Dr. O’Dell:** You made an interesting and valid observation about balance studies, namely that the shifting of the requirement for balance depends on nutritional status. In view of these observations, I have two questions. How should one do a balance study in the human? Because at present we have no other method for assessing requirements in adults, how should we determine bioavailability of trace elements?

**Dr. Mertz:** We can continue to do our balance studies the way we have done them so long as we interpret the results with caution. The results of balance studies tell us what we need in order to maintain our present nutritional status, e.g., high or low body stores. If you want to look at the true requirement, however, you would have to feed the subjects a diet very low in that particular element so that you achieve the obligatory excretion and wait long enough until the excretion has stabilized. That one could be interpreted as the absolute minimum requirement. This is not identical with what we should recommend as intakes. I would hope that perhaps in 10 years we will have a better measure for determining the requirement than now, e.g., assessing nondestructively trace element concentrations at their specific sites.

**Dr. Hurley:** I would like to comment again on Dr. Thompson’s difficulty with the problem of differentiating between depletion and deficiency. I think, Dr. Mertz, that you hit the nail on the head with last response, but then the nail went sideways. You said that there has to be some depletion of specific sites, and I think that is the crucial point. Obviously, if some functional defect is seen, there has to be a biochemical defect as well. If we are talking about the absence or inadequate amount of a trace element, it is reasonable to suppose that
at a specific site where that function is carried out and the element is required, the absence
or the inadequate amount of the element will result in defective function. However, if we
knew in each case what the particular problem was, then we might be able to measure it—
might, if we could measure it in specific local sites. In most cases, we cannot do that as
yet. So what we are left with is measuring, for example, the amount of zinc in the liver or
some other organ or even in the whole body. Obviously, though, if a specific compound is
what is important and is the one that is inadequate, its deficiency could be completely
obscured by measuring the whole tissue. Therefore we will not see total depletion, but we
may see a very profound effect on function.

Let me give an example from our own work in the pregnant rat. The plasma zinc level of
a rat given a zinc-deficient diet at the beginning of pregnancy declines by as much as 50%
within the first 24 hr, in fact in much less than 24 hr. That, you may say, Dr. Thompson,
is an example showing that plasma zinc does not mean anything. However, do not forget
that it may mean a great deal to the developing embryo, because the plasma is its only
source of zinc, ultimately through the placenta but also earlier in the preimplantation embryo.
We have shown that after as little as 3 days of a zinc-deficient diet in the pregnant rat the
preimplantation embryo is already morphologically defective. That pregnant rat does not
have an overall body depletion of zinc; if it has any decrease, it is so small that we probably
cannot measure it. Certainly, all the tissues that we have measured are normal in concen-
tration, but the plasma zinc is low, the uterine fluid zinc is low, and therefore the embryo
is affected.

Dr. Mertz: I have two of my own examples on this important point. When I want to
assess the chromium status of a person whom I know is chromium-deficient, I find no
differences in serum chromium whatsoever. When I am interested in the cobalt status of a
person severely ill from pernicious anemia, again I find no differences in cobalt levels. Both
cases are similar in that the important, biologically active species of an element is drowned
in an ocean of other forms that are useless for the organism. I believe that if we can make
progress in speciation of trace elements in tissue fluids and organs, this will help us to
establish better diagnostic measures.

Dr. Gebre Mehdin: I have the impression that trace elements are not different from other
nutrients such as vitamin A. When you reduce the vitamin A intake, the circulating levels
go down first but then go up again, evidently to try and provide target cells with as much
vitamin A as possible without appreciably influencing the depot. This process goes on until
the intake becomes critical, and then the depot begins to go down. At this stage normal
circulating levels can be maintained despite nearly depleted stores. So evidently, as has been
mentioned, we are not quite ready to say what depletion and deficiency is in respect to
several nutrients.

Dr. Mertz: My first statement would be that the degree of our knowledge of trace element
metabolism has a tremendous spread. We know nothing about some, and we know much
about others. This is a very important statement. We can talk about tissue stores quite
intelligently for iron. When it comes to zinc, we know much less. We really do not even
know what the functioning storage organ or pool might be for zinc. What I am saying is
that the science has not yet advanced to that point where one can give the practitioner
practical guidelines for all trace elements.

Dr. Thompson: Could I come back to the two points that Dr. Hurley brought up. I never
said plasma zinc was useless. The problem with it is that many other things affect it, among
which is the affinity of albumin. Dr. Hurley rightly says that there is transfer of free zinc
across the placenta, so by altering the plasma level of zinc its transfer across the placenta
could be increased, and this must be true for other tissues. What I did say was that so many things can affect an individual plasma zinc level that you cannot say that a particular individual is or is not zinc-depleted. I was also pointing out that it may be true, but I am not sure how well proved this is, that the measurable tissue or body concentration of zinc can be unaltered. Somewhere in the body, perhaps in an enzyme, there may be a small reduction of zinc which turns something off and limits growth.

Dr. Diplock: I would like to make a point which concerns the three-corner relationship between selenium, silver, and vitamin E. If you treat any normal animal with silver, the animal survives perfectly well, and the serum level of selenium does not change. If you now remove vitamin E from the diet of the animal and do the same experiment, the animal dies rapidly; the serum level of selenium, if anything, rises, although the silver toxicity is manifested through complexing available selenium. This I think illustrates how unreliable in an acute clinical situation measurement of the serum level of an element can be. Removal of the vitamin E increases the oxidative stress within the liver. Under normal circumstances, this would be met by glutathione peroxidase; but when silver is administered, the activity of glutathione peroxidase is suppressed, as silver complexes with selenium, and the animal dies before selenium can be mobilized from elsewhere by whatever homeostatic mechanism exists to control the levels of intracellular selenium.