Clinical Deficiencies: When to Suspect There Is a Problem

K. Michael Hambidge

Department of Pediatrics, University of Colorado, Health Sciences Center, Denver, Colorado 80262

Despite notable recent advances in our appreciation of the role of trace elements in human nutrition and disease, clinical detection of trace-element-deficiency states usually remains extraordinarily difficult. There are several outstanding reasons for the continuing difficulties in diagnosis. These include a lack of specificity of symptoms and signs of individual trace deficiencies, a lack of sensitive reliable laboratory assays for the detection or confirmation of trace deficiencies, and continuing uncertainty about the occurrence of human deficiencies of some of the "newer" trace elements. If such deficiencies do occur, their clinical presentation in man has not been documented. Despite the recent growth of interest in and the expanding list of trace elements of probable or proved mammalian nutritional importance, there are relatively few of these that we know with certainty can be associated with deficiency diseases in man. Nevertheless, experience gained over the past 20 years indicates that we cannot afford to be complacent about the role of trace elements in human nutrition and disease, even in the case of those elements for which no specific roles have yet been identified.

Meanwhile, the trace elements that have been shown to be associated with human deficiency diseases and which provide a basis for this discussion are seven or eight in number. These are iron, iodine, zinc, copper, selenium, molybdenum, chromium, and possibly manganese. With the exceptions of iron, iodine, and severe zinc deficiency, clinical identification of a deficiency of these trace minerals cannot be achieved without a very high index of suspicion. The circumstances in which such suspicion might reasonably be aroused provide the basis of this discussion.

CLINICAL FEATURES

Diagnostic or Strongly Suggestive Features

Historically, early recognition of the clinical importance of iron and iodine deficiencies is attributable in part to the distinctive nature and the ease of clinical detection of these deficiency diseases. Each of these entities has features that are attributable primarily to a more or less specific disruption of a single organ system. Although the clinical features of iron-deficiency anemia, hypothyroidism, or en-
demic cretinism are easy to identify clinically, it is worth noting, especially in the context of subsequent discussion on milder trace-element-deficiency states, that this does not apply necessarily to early or mild iron- and iodine-deficiency states. Thus, for example, the prenatal effects on the fetus of milder forms of maternal iodine deficiency during pregnancy may be difficult to diagnose in the presence of only subtle effects on central nervous system development and function (1). Similarly, adverse effects of mild, early iron deficiency have been found to precede any evidence of iron-deficiency anemia (2). Again, these effects are not easy to detect clinically.

Apart from iron- and iodine-deficiency states, the only other trace deficiency that is now relatively easy to recognize clinically is severe zinc deficiency. This may occur as a result of acquired zinc deficiency; for example, in patients maintained on intravenous nutrition without adequate zinc supplementation. It may also occur as a result of at least one inherited defect in zinc metabolism: acrodermatitis enteropathica (3). The total body depletion of zinc in these clinical circumstances may in fact be quite small (4); however, if only because of the clinical consequences, this is rightly regarded as the severest human zinc-deficiency state. Many organ systems are involved in this fascinating disorder, but clinical diagnosis owes its simplicity to one specific feature: the often dramatic epithelial involvement with a skin rash of characteristic distribution primarily at the extremities and around the body orifices (Fig. 1).

Nonspecific Features

Trace element deficiencies present more commonly with nonspecific clinical features. Combinations of nonspecific features may arouse suspicion of a specific

FIG. 1. Acrodermatitis enteropathica.
trace-element-deficiency state, which would be strengthened in the right etiological circumstances or in combination with abnormalities of certain ancillary investigations.

Perhaps the most frequently occurring of these nonspecific features is weight loss or, in the case of infants and children, failure to achieve maximal growth potential. Zinc is the most outstanding single element in this context. Severe zinc deficiency, as in acrodermatitis enteropathica, causes abrupt cessation of growth in the infant. A more moderate degree of zinc deficiency has been associated with dwarfism and delayed sexual maturation in adolescents (5). An increase in lean body mass in young children recovering from protein-energy malnutrition in Jamaica appears to be adversely affected by zinc deficiency (6). Skeletal growth may be impaired by mild zinc deficiency in young children in North America (7). Very little is yet known about the effects of maternal zinc deficiency on fetal growth and development in the human, but experimental maternal zinc deficiency in animals has a wide range of adverse effects on fetal growth and development (8). Copper deficiency may cause failure to thrive in premature infants (9). The rate of weight gain of malnourished Turkish infants has been reported to be accelerated by chromium supplementation during the recovery phase (10). Weight loss has been attributed to chromium deficiency in an adult receiving long-term parenteral nutrition (11). Diminished physical growth has been reported to result from experimental induction of deficiencies of several of the "new" trace elements in animals. These include nickel, vanadium, silicon, arsenic, lead, and possibly tin and fluorine. The possibility that at least some of these observations have clinical relevance in humans merits continuing consideration, especially in circumstances that predispose to multinutrient-deficiency states.

There is growing interest in the roles of individual trace elements in the integrity of the immune system. In humans, deficiencies of both iron and zinc have been shown to have specific adverse effects on the immune system (12). More extensive experience with experimental animals suggests that other trace deficiencies will be found to be important in the integrity of the immune system in humans.

Central nervous system function is affected adversely by several specific trace element deficiencies. Iron deficiency may affect behavior, even when not sufficiently severe to cause anemia (2). Behavioral abnormalities, especially loss of hedonic tone, are a notable feature of acrodermatitis enteropathica and other severe zinc-deficiency syndromes (13). Severe de facto copper deficiency in Menkes' steely hair syndrome is associated with fatal central nervous system disease. Milder nutritional copper deficiency has been reported to involve the central nervous system in premature infants. Severe chromium deficiency has been associated with abnormal function of the central and peripheral nervous systems (11). Headaches, lethargy, night blindness, and coma have been reported in association with human molybdenum deficiency (14).

Other organs systems known to be affected by more than one trace element deficiency are the gastrointestinal, cardiovascular, hematological, and musculoskeletal systems. Diarrhea occurs in severe copper- and zinc-deficiency states.
Feeding problems, constipation, and/or prolonged jaundice are among the most frequent early manifestations of congenital hypothyroidism. Severe selenium deficiency is associated with a potentially fatal cardiomyopathy in Keshan's disease (15). Human copper deficiency may conceivably cause cardiac arrhythmias (16), and tachycardia occurs in molybdenum deficiency (14). In hypothyroidism there is bradycardia, poor peripheral circulation, and cardiomegaly. Anemia occurs in iron-, iodine-, and copper-deficiency states. The iron-deficient subject has flabby musculature and decreased ability to perform muscular work. Various disorders of the skeletal muscles, including severe hypotonia, occur in hypothyroidism. Preterm copper-deficient infants may be hypotonic. Incapacitating muscular pain has been described as a consequence of selenium deficiency (17). Anorexia and/or pica are commonly present in iron deficiency, and decreased food intake is a noteworthy feature of zinc deficiency (18). Several trace elements, for example, zinc, copper, and nickel, have been linked to the special senses of taste (19). Skin lesions are characteristic of many nutritional deficiency states, including those of zinc and copper. Zinc deficiency can cause several other epithelial disorders, including alopecia, gingivitis, and nail dystrophies. This brief review is not intended to provide comprehensive documentation of the clinical signs and symptoms of trace element deficiency states but, rather, to illustrate the extent and diversity of these features as well as the overlap among features of individual trace deficiencies.

ANCILLARY INVESTIGATIONS

Trace element deficiencies may also be suspected, or indeed diagnosed, as a result of investigations that have been ordered for reasons other than the attempt to diagnose a specific trace element deficiency. Combined deficiencies of xanthine oxidase and sulfite oxidase are manifested, for example, by abnormally low uric acid levels in serum and urine, low urinary excretion of sulfate, and elevated urinary excretion of sulfite and thiosulfate. These findings are pathognomonic of molybdenum deficiency (14) or an abnormality of molybdenum metabolism (20). The characteristic early features of copper deficiency are hematological and radiological in nature, specifically a microcytic anemia, neutropenia, and osteoporosis. The combination of two or more of these features in the right etiological circumstances is highly suggestive of copper deficiency. More specific radiological findings may be evident in severe copper-deficiency states (21). The possibility of a deficiency of this trace metal is unlikely to be entertained should these ancillary investigations not be performed. As another example, chromium deficiency is very unlikely to be considered unless there is evidence of impaired glucose tolerance (22) or possibly abnormalities of lipid metabolism (23).

LABORATORY DATA CONCERNED MORE DIRECTLY WITH TRACE ELEMENT STATUS

This section approaches closely the subject covered by the next chapter and so discusses it only briefly here. In a research setting there are a variety of measurements that can be and have been made, the results of which may give valid rise to
suspicions that a trace element deficiency exists but which falls short of establishing a diagnosis. Alternatively, there may be a combination of factors emerging from a study that point toward the existence of a specific trace element deficiency. For example, the observation that plasma zinc concentrations of breast-feeding mothers recover slowly from the hypozincemia of pregnancy and subsequently decline again with prolonged lactation unless the mothers receive a small daily dietary zinc supplement (24) suggests that mild zinc deficiency may be common in lactating women in North America. The fact that the small zinc supplement was associated with higher zinc concentrations in breast milk suggests that this deficiency is of nutritional importance.

Hair analyses merit brief mention in the context of this section. Use of hair analyses in the diagnosis of individual trace deficiencies has no valid basis, at least at this time (25); however, the association of low hair concentrations of specific trace elements on a group basis and certain clinical features or diseases may increase suspicion about the possibility of an underlying trace deficiency. For example, the association of low hair zinc, low growth percentiles, poor appetite, and hypogeusia was the first indication that a growth-limiting mild zinc-deficiency state could affect otherwise healthy, well-nourished children in the United States (26).

**RESPONSE TO DIETARY SUPPLEMENTATION WITH A SPECIFIC TRACE ELEMENT**

Laboratory assays are frequently of limited or no proven use in the detection of mild trace-element-deficiency states. In these circumstances, the only recourse may be a trial of dietary supplementation with the specific trace element that is suspected to be deficient on clinical grounds. Such trials are time-consuming and provide only retrospective confirmation of a deficiency state; however, if supplementation is associated with a physiological or clinical response, this approach may provide the most convincing evidence attainable of a preexisting specific trace-element-deficiency state. Moreover, such a response would indicate that the deficiency is of physiological and clinical significance.

The value and reliability of these dietary supplementation studies are dependent on a number of key factors. First, the dose of the supplement given must be physiological and should normally be of the same order of magnitude as that provided by a satisfactory diet. Second, the clinical, physiological, and/or biochemical parameters that are monitored should be parameters that are affected by the nutritional status of the specific trace element under investigation. At the outset these parameters would be expected to be "low" or "low normal." There must be no pharmacological effect of the nutrient under investigation on the parameters that are being monitored. Finally, the study must be undertaken under strictly controlled conditions.

In Denver, a number of dietary zinc-supplementation studies have been completed or are in progress (27). In each of these, the mean increment in linear growth in zinc-supplemented infants or children was significantly greater during the study period than the corresponding increments for placebo-treated subjects. Target pop-
ulations for these studies have included normal formula-fed infants (28) and young children with relatively low height-for-age percentiles (7,29). Zinc supplementation has also been associated with significantly greater increases in food intake (18) (Fig. 2). Impaired physical growth rates and decreased food intake are the earliest and most prominent features of experimental zinc deficiency in young animals. In these human studies, very small quantities of zinc were administered under double-blind-controlled conditions. Zinc has no pharmacological effect on growth. Therefore the results of these studies have been interpreted to indicate a preexisting growth-limiting zinc-deficiency state in the children studied. This was a laborious approach to diagnose or confirm zinc deficiency, but neither the plasma zinc level nor any other laboratory index of zinc status was sufficiently sensitive to be of value in these circumstances. Moreover, the supplementation studies not only indicated the existence of a zinc-deficiency state but demonstrated the practical importance of this deficiency in limiting physical growth and impairing appetite.

ETIOLOGICAL CIRCUMSTANCES

In general, it is apparent that the clinical features of trace element deficiencies are alone unlikely to arouse suspicion of the existence of an underlying trace-element-deficiency state. The knowledgeable clinician, however, may be alerted by these signs and symptoms in the presence of the right etiological circumstance. To illustrate this point with an extreme example, severe deficiencies of zinc, copper, chromium, molybdenum, and perhaps selenium have each been documented in patients maintained on prolonged intravenous nutrition without adequate trace element supplementation. A high index of suspicion of possible trace element deficiencies is therefore obviously justified in such circumstances in the presence of features that are known to be consistent with a specific trace element deficiency.

![FIG. 2. Mean increases in calculated dietary intakes between the beginning and end of a 1-year study period. Intake for test subjects does not include zinc supplement. Participants were 30 children aged 2 to 6 years with low height-for-age percentiles. Daily zinc supplement averaged approximately 0.3 mg/kg body wt/day. Analysis of variance indicated a significant (p<0.05) treatment effect for energy, protein, and zinc (18).]
Moreover, in view of the ever-growing number of newly identified trace element deficiencies in such patients and of our very incomplete knowledge of the possible clinical effects of "new" deficiencies, the possibility of such a deficiency always merits consideration in the presence of unexplained symptoms and signs. Synthetic and semisynthetic diets administered orally, as well as those given intravenously, may be deficient in one or more trace elements. Selenium levels, for example, are generally low in low-phenylalanine formulas designed for use in the treatment of phenylketonuria (28).

These are straightforward examples, but in general the subject of etiological circumstances is one of growing complexity, attributable primarily to the extraordinary diversity of factors that have now been indicted in the etiology of trace element deficiencies (Table 1).

<table>
<thead>
<tr>
<th>Trace element deficiencies: etiological factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inborn errors of trace metal metabolism: Fe, Zn, Cu, Mo</td>
</tr>
<tr>
<td>2. Intravenous nutrition: Fe, Zn, Cu, Se, Cr, Mo</td>
</tr>
<tr>
<td>3. Oral synthetic diets: Zn, Se</td>
</tr>
<tr>
<td>4. Multinutritional deficiency states: Fe, Cu, Zn, Cr, Se</td>
</tr>
<tr>
<td>5. Prematurity: Fe, Cu, Zn, (Se), Cr</td>
</tr>
<tr>
<td>6. Malabsorption state/diarrhea: Zn, Cu</td>
</tr>
<tr>
<td>7. Excessive losses: Zn, Cu, (Cr)</td>
</tr>
<tr>
<td>8. Iatrogenic: Zn, Cu</td>
</tr>
<tr>
<td>10. More widespread nutritional deficiencies; contributory factors include losses in food processing, poor bioavailability, and relatively high requirements, e.g., during rapid growth, pregnancy, and lactation: Fe, Zn</td>
</tr>
</tbody>
</table>

One of the most important and obvious circumstances is that of multinutritional deficiency states. For example, deficiencies of several trace elements have been reported in association with protein-energy malnutrition. These have been highlighted by the studies of zinc status of malnourished children at the Tropical Metabolism Research Unit in Jamaica. The possibility of additional clinically important trace element deficiencies in these circumstances has been proposed (29).

The very-low-birth-weight premature infant provides another important, albeit very special, example of an individual whose clinical course is frequently complicated by multinutritional, including trace element, deficiencies. With improved mortality figures and advances in treating the pulmonary disease of the very premature, adequate nutritional management has become a growing challenge. For example, the premature infant does not start postnatal life with the hepatic copper stores that are available to the infant born at term. Copper-deficiency syndromes have been identified in very-low-birth-weight infants when fed with relatively low copper formulas (9). Zinc balance appears to be exceptionally unfavorable in the low-birth-weight infant (30,31). In special circumstances, the increased risk of zinc deficiency has been shown to be of great clinical significance in this population;
However, the clinical importance of milder degrees of zinc deficiency in the premature infant remains to be established.

For a variety of reasons, multiple nutritional deficiencies are now known to be common in our hospitalized population at all ages. Sometimes these are clinically obvious; at other times they are more subtle. Once again, trace element deficiencies have to be considered. For example, severe zinc- and copper-deficiency states have been documented in patients with intestinal malabsorption syndromes. Circulating manganese concentrations have been reported to be unusually low in these circumstances. Excessive losses of specific trace elements occur in a variety of pathological circumstances and may lead to clinically significant deficiencies of specific trace elements. For example, severe zinc deficiency has been reported with prolonged use of the chelating agent penicillamine due to chronic hyperzincuria. Hyperzincuria is also a feature of any catabolic state and a variety of diseases, including diabetes mellitus and various hepatic disorders. Urinary chromium losses may be excessive in diabetes. Unusual losses of trace elements may occur via other routes, including the gastrointestinal tract, and via sweat, exudates, and hemorrhage.

The discussion of etiology has focused so far primarily on circumstances predisposing to multiple-nutrient, including multi-trace-element, deficiencies; however, trace element deficiencies can and indeed frequently do occur in isolation. A very special example of this is provided by inborn errors of trace element metabolism (3). Specific deficiencies of zinc, copper, iron, and, in practice, of molybdenum have been traced to inborn errors in the metabolism of these metals. In experimental animals, inborn errors of metabolism of other trace minerals have been documented, for example, manganese and probably chromium, and there can be little doubt that an increasing number of inborn errors of trace mineral metabolism will be recognized in the years to come in the human being. This possibility should be suspected especially when there is a familial disease of unknown origin presenting during either adulthood or childhood, even though the clinical features may not be diagnostic or even very suggestive.

Specific nutritional deficiencies of a single trace element may occur in certain geochemical environments. The classical example is of course, endemic goiter due to iodine deficiency. Keshan disease, which is characterized by a cardiomyopathy that can be fatal and that occurs in an extensive geographical area of China, is attributable primarily to a deficiency of selenium (15). Better knowledge of the geochemical environment in certain areas of the world may lead to the identification of other trace element deficiencies, although this is unlikely to be very productive in the western world, where the supermarkets provide foods from many different areas.

Nutritional deficiencies of one or more trace elements are not necessarily limited to any one geographical area. Iron deficiency is one of the most common of all diseases and occurs worldwide. There are now strong indications that zinc deficiency is also common in some sections of the United States population, and there are suggestions that chromium deficiency may be common in the adult population of the United States. Certain sectors of the population may be more susceptible to
suboptimal trace nutritional status. These include infants, children, and adolescents during periods of rapid growth; pregnant and lactating women; and the elderly. Those who depend on or choose to consume diets composed of highly processed foods may be especially vulnerable, and this applies in particular to the formula-fed infant whose one or major food staple is a highly processed product. Factors that adversely affect bioavailability may also impair trace element status. These may occur "naturally" in foods consumed, e.g., phytate and fiber, or may result from food processing. For example, the quantities of iron used to fortify infant formulas in the United States are sufficient to impair zinc status (32). A similar problem appears to apply during pregnancy as a result of antenatal iron supplements or therapy (33). In our present state of knowledge, it therefore appears necessary to have a high index of suspicion in a wide range of circumstances in order to avoid the risk of missing a diagnosis of a clinically significant trace element deficiency.

CONCLUDING REMARKS

In clinical practice there is a finite limit to the attention that can be devoted to the possibility of a trace element deficiency(ies). Current priorities for attention are the more florid clinical features, as in severe zinc deficiency, and the most apparent clinical circumstances for severe trace element deficiency status, for example, prolonged intravenous feeding. Nevertheless, the major clinical importance of the trace elements may well be proved to result from the widespread occurrence, at least in some populations, of certain milder trace element deficiency states, resulting in problems with normal growth and development and perhaps contributing to some of the major public health problems of this generation. In some instances, for example, zinc and possibly chromium deficiency, we are beginning to appreciate some of the circumstances in which such widespread deficiencies may occur. The lack of specific clinical features, however, is a considerable handicap in the detection of these deficiencies, and research progress may well depend primarily on improved diagnostic tools suitable for use on a population-wide, as well as in an individual, scale.

ACKNOWLEDGMENTS

This work was supported by grant 5 R22 AM12432 from the National Institutes of Arthritis, Metabolic, and Digestive Diseases and by grant RR-69 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.

REFERENCES

DETECTION OF CLINICAL DEFICIENCIES


DISCUSSION

Dr. Chandra: Dr. Hambidge, you have used increased growth following supplementation as one of the indicators of zinc deficiency. Is there a possibility that giving trace element supplements may enhance growth whether or not there is an underlying deficiency? In another situation, an improved immune response after supplementation with zinc does not mean that there was necessarily a deficiency of the trace element. We may be seeing a pharmacological effect. Does zinc increase somatomedin production?

Dr. Hambidge: Carefully controlled, randomized supplementation studies with physiological quantities of zinc are the most reliable means available to confirm a preexisting mild zinc deficiency state. One point that merits particular emphasis with respect to our experience with zinc supplementation studies and their effects on growth is the extraordinarily small quantities of zinc that have been administered. These are clearly physiological quantities, and it is very difficult to conceive that we are getting a pharmacological effect on growth from these very small quantities of zinc, quite apart from the fact that there is no evidence that one can get a pharmacological effect of zinc on growth. The lack of adequate laboratory assays for the detection of mild zinc deficiency remains a major limitation.

Dr. Prasad: You indicated that perhaps the severity of acrodermatitis enteropathica could be correlated with plasma zinc. Are plasma zinc levels of less than 40 μg/dl truly indicative of severe deficiency? The problem is that in a few cases that have been reported in the literature, despite the presence of acrodermatitis enteropathica skin lesions, the plasma zinc levels were not that low.

Dr. Hambidge: In my experience, skin lesions have not been observed until the plasma zinc concentration falls below 40 μg/dl (6 μmol/liter). I have no personal experience with "acrodermatitis enteropathica" with normal plasma zinc concentrations. Great care is needed to ensure against the risk of sample contamination.

Dr. Lombeck: I agree with this. If we have to put a limit somewhere, I would say that very severe skin lesions occur at levels below 35 to 40 μg/100 ml of plasma in patients with acrodermatitis enteropathica and in patients with Crohn's disease.

Dr. Prasad: My comment has to do with the widely held concept that alleged clinical features of zinc deficiency must be reversed by physiological levels of zinc supplementation if indeed zinc deficiency is responsible for those features. As a hematologist, when I see a patient with iron deficiency anemia I begin treatment with 1 g of ferrous sulfate a day, which supplies 330 mg of iron, and in 4 weeks time I correct the hemoglobin from 7 g% to 14 g%. If I were to take the same patient and give only a physiological amount of iron, say perhaps 10 or 15 mg daily, the anemia would not be corrected even after 1 year. Inasmuch as the physiological amount of iron supplementation did not result in correction of anemia, should I conclude that iron is not physiologically important for hemoglobin synthesis?

Dr. Hambidge: In contrast to the situation with zinc, several laboratory procedures are very useful in the diagnosis of iron deficiency. Confirmation of mild zinc deficiency is dependent on the results of physiological levels of zinc supplementation under controlled conditions.
Dr. Chandra: It may well be that there is a continuing loss of zinc in many iron-deficient patients; that is why you need a much larger dose of zinc to correct the deficiency in 4 weeks.

Dr. Prasad: I did this experiment many years ago, and some patients in Iran had no blood loss at all: It was all nutritional, and I observed no change in the hemoglobin concentration with physiological amounts of iron. I will give you another example. In an experimental human zinc-deficient model, I supplemented physiological amounts of zinc in the order of 10 to 15 mg a day after institution of a zinc-restricted diet for 6 months to human volunteers. With this degree of supplementation, it took us nearly 6 months to observe an increase in the plasma testosterone level. If I had terminated my experiment after 3 months of zinc supplementation I could have erroneously concluded that zinc had no role to play in male hypogonadism.

Dr. Golden: Your point about the differences between physiological and pharmacological doses is important because, particularly with zinc, it is the only way we have at the moment of making the decision about whether there is a deficiency. I think that with any trace element, and certainly with zinc, that there is not a linear relationship between the dose and the response. In my experience, as we increase the dose to pharmacological levels we begin to get deleterious effects of supplementation rather than advantageous effects. If you are actually correcting a deficiency you are likely to see an increase of, say, growth with supplementation; as you add more, you begin to get inhibition of growth: I have seen children whom we supplemented with very high levels of zinc (10 mg/kg/day) have inhibition of growth with these high levels of zinc, presumably because of one of the interactions which take place, such as zinc-induced copper deficiency. Therefore I am very surprised to hear you say that when you give zinc and there is an improvement in white cell or immunological function that you do not think there was preexisting zinc deficiency and that you ascribe this to a purely pharmacological effect.

Dr. Chandra: If you give 200 to 300 mg of zinc sulfate to healthy individuals with normal zinc nutrition in terms of zinc levels in plasma hair and nails, there is an increased response of lymphocytes to mitogens and antigens. This is a known pharmacological effect. In vitro, a progressive increase of zinc up to a certain limit produces supernormal lymphokine release and DNA synthesis in lymphocytes. After a certain threshold is reached, if you add more zinc there is a deleterious effect, in vivo and in vitro.

Dr. Golden: This is a very important point because if you happened to have lived in fifteenth century England it was normal to be 4 feet 8 inches. If you happened to live in Egypt, it is normal to have schistosomiasis. The equation of what usually happens with what is normal and with what is optimal is not necessarily correct. The problem is the definition of “normal,” “usual,” “optimal,” “desirable,” etc.

Dr. Zoppi: You compared breast-fed infants with formula-fed infants supplemented with zinc. In both groups of infants, the balance of zinc is negative. How can you explain this fact?

Dr. Hambidge: In our experience, if more zinc is added to the formula, it is excreted in the feces.

Dr. Guesry: Do you have any information concerning the time when the balance becomes positive? This may help to understand the reason why the balance is negative during the first days of life.

Dr. Hambidge: Our experience is very similar to that of Jonathan Shaw in London. It takes about 2 months on average to achieve positive zinc balance. Results of recent balance studies on very-low-birth-weight preterm infants in Toronto were quite different. I do not
have an explanation for this, but it is clear that we need additional studies with more sophisticated techniques.

Dr. Mertz: I would like to come back again to this question of what is normal and what is a "physiological" versus a "pharmacological" effect. When one talks about a normal iron status, one cannot refer to an average iron status of a population group and take this as normal. The only way to define a normal iron status is that used by Garby et al. many years ago. They supplemented Swedish women with physiological doses of iron over extended periods of time until hemoglobin levels became stable. That final hemoglobin level, obtained with optimal iron intakes was considered the "norm." I wonder if the effects that you observed could not have been true physiological effects superimposed on a deficiency that you were unable to diagnose by available methods. The reason I am suggesting this possibility is that this retrospective diagnosis of a marginal deficiency by response to supplementation is very important to the nutritionist, because for many trace elements it is the only diagnostic method we have.

Dr. Aggett: I would like to comment on the spectrum of zinc deficiency and relating the symptoms to levels of plasma zinc. The symptoms of acrodermatitis as encountered in patients with total parenteral nutrition can be manipulated quite considerably: Anorexia, for example, can be dependent on the protein intake; normal plasma zinc levels can accompany quite extensive skin lesions especially when the patients are in negative nitrogen balance. Furthermore, the skin rash can be modified by the supply of unsaturated fatty acids.

Dr. Gebre Mehdin: I would like to expand the discussion into the area of metal-transport proteins and the characterization of our patients in this respect. In Uppsala we find that most of the variation in zinc status, and for that matter a number of other trace elements, can be accounted for by variations in serum transport proteins. I am not suggesting that there is a simple relationship between a mineral and a transport protein. The interesting thing is that when you normalize the transport protein, e.g., α₂-macroglobulin, prealbumin, or retinol-binding protein, the trace element levels normalize automatically on a diet with reasonable nutrient density to which no extra mineral elements have been added. This applies also to pregnant women in whom there are physiological variations in protein synthesis that influence trace elements. We believe it is important to take into account the total metabolic situation of these children. In this respect, inflammatory processes, whether subclinical or overt, may play a much more important role in variations in trace element status than does probably dietary intake.

Dr. Hambidge: In pregnant women we observed a significant decline in plasma zinc concentration very early in gestation. I think this is before there are any changes in potentially important transport proteins for zinc.

Dr. Chandra: In our experience, the changes in concentrations of transport proteins predate the changes in trace element levels.

Dr. Zlotkin: Dr. Hambidge, would you agree that it is very difficult to make a free living child in the western world zinc-deficient? I am also quite concerned about your use of the term mild zinc deficiency without being able to define the term more specifically. The fact, for example, that zinc levels fall during the first year of life may reflect a normal physiological phenomenon rather than a deficiency state. We do not see normal full-term babies with zinc deficiency.

Dr. Hambidge: I agree that the decline in milk zinc concentrations with duration of lactation is a physiological phenomenon. I was merely pointing out the difference in the rate of decline between two groups, in one of which the mothers had received a physiological zinc supplement and in the other they had not. I do, however, take issue with your statement
that we do not see zinc deficiency in normal full-term infants in the United States. There is a lot of evidence now to the contrary: for example, the differences in plasma zinc for breast-fed versus formula-fed infants and for those receiving an iron-fortified formula versus those who do not. I have already discussed other, more compelling, evidence for the occurrence of zinc deficiency in otherwise normal infants and children.

**Dr. Bergmann:** Infant formulas marketed in the United States have mandatory trace element fortification on the basis of current knowledge. Most of the European formulas do not have any trace element fortification. The Codex Alimentarius recommends fortification by trace elements, and the European Economic Community is preparing a standard that will go into legislation requiring fortification, actually without knowing the trace element situation in the normal infant population in different European countries. I am somewhat reluctant to accept a blind fortification of infant formulas.

**Dr. Hambidge:** This is a very important topic. We may be faced with as many potential problems at the moment with fortification programs for infant formulas as we would be if nothing was added to these formulas. Great care needs to be taken to ensure that we do not fortify to too great an extent; I am concerned that this may be true with iron in the United States, with consequent deleterious effects, for example, on zinc status.

**Dr. Bergmann:** I have been very much concerned about the iron nutritional status in Germany. Iron deficiency being the most prevalent single nutritional deficiency in developed countries, I studied the prevalence of iron deficiency of some 400 German infants and children, at times when iron fortification of infant foods or prophylactic iron supplements were uncommon. I found just one hemoglobin value below 10 g/dl. In the United States the incidence would have been much higher with respect to this parameter. I do not see any reason in our country to fortify infant formulas without knowing that a certain part of the infant population needs the additional iron. Considering the other trace elements, I prefer to look at the problem on an individual basis, rather than recommending general fortification by those elements.

**Dr. Hambidge:** If I could respond briefly, I think we are too concerned with fortification programs at this time. However, there is also the concern of very low levels occurring as a result of the processing of the original cow's milk in the manufacture of the formula. We do not have enough data to always make the correct decision at this time.

**Dr. Golden:** Concerning the earlier comment I made about very large doses of zinc—when we were giving our children the dose Dr. Prasad was talking about—we were galvanizing them. We now find that we do get increases in rates of weight gain (I think we should not talk about growth when we are talking about weight gain). We get these changes in rates of weight gain without any changes in intake so that there is an alteration in the efficiency of growth. It seems that we only get profound appetitive effects with concomitant high protein intakes. There is a very good reason for this in the hyperammonemia and the changes in the Lowenstein cycle with zinc deficiency. If you then start to push these with a high protein intake, you produce nausea and loss of appetite; if the protein intake is not high, this effect is not seen.

**Dr. Delange:** I would like to comment briefly on a point which has been raised regarding legislation on supplementation of oligoelements in the infant diet. My specific interest in trace elements is iodine and thyroid disorders resulting from an extraphysiological supply of iodine. The disorders resulting from iodine deficiency have been known for centuries and are still prevalent in several European countries. Consequently, legislation on iodine supplementation is required and exists in some European countries, e.g., Switzerland. However, such legislation can be difficult to propose and control because (a) the requirement for
oligoelements is not always accurately known; (b) there can be marked regional variations in the dietary supply of some oligoelements within a country, making nation-wide supplementation difficult; (c) there can be slow changes in food habits in the country, which has been shown in Switzerland where a decreasing consumption of salt, which is the vehicle for iodine, resulted in a slight relapse of iodine deficiency (Schmid et al. Schweiz Med Wochenschr 1980;110:1209); (d) conversely, uncontrolled supplementation of iodine from various origins can drastically increase the iodine intake independent of programs of supplementation. Consequently, periodic reevaluation of the effects of supplementation in oligoelements is necessary, as performed in Switzerland (Eberhard et al. Schweiz Med Wochenschr 1983;113:24).