Perusal of most medical textbooks shows that childhood malnutrition in the tropics has been consistently ascribed to feeding a diet deficient in either protein or energy, or some combination of the two. Kwashiorkor is said to result from "pure" protein deficiency, whereas marasmus arises from protein and energy deficiency. These concepts are enshrined in the term protein-energy malnutrition.

We now know that the malnutrition of these children is much more complex and is unlikely ever to be the result of "pure" protein deficiency (1). Lack of other essential dietary components, toxins in fresh and spoiled food, and the grossly disturbed relationship between the child and his flora are all now thought to play central roles in the genesis and maintenance of malnutrition. To this must be added the role of infection with recognized pathogenic organisms, which nearly always precipitates and usually accompanies malnutrition (2).

Of the dietary components, the individual essential amino acids, the vitamins, and the major electrolytes have received most attention, whereas fats, nonelectrolyte minerals, and the trace elements have been relatively neglected. Past reports of abnormalities in metabolism of these nutrients have been viewed as being superimposed on the primary defects of protein and energy deficiency.

The view that the other deficiencies are epiphenomena is supported by consideration of xerophthalmia. In some parts of the world most children with malnutrition have xerophthalmia, whereas it is very uncommon in other geographic locations. This difference in clinical signs posed a problem as to whether clinicians were dealing with two pathological entities. The recognition that xerophthalmia was specifically caused by vitamin A deficiency resolved the conundrum: Now it is said that in some parts of the world malnutrition is complicated by superimposed vitamin A deficiency, whereas it is not a complicating factor in other locations; therefore it is not an integral part of the condition. Trace element deficiencies have been considered, analogous in this regard to vitamin A deficiency, as nonessential epiphenomena.

Recently, the central dogma of protein deficiency as the dominant cause of kwashiorkor has been challenged. The basis of this challenge is that the sine qua non of kwashiorkor—nutritional edema—can resolve without any change in plasma...
albumin concentration (3) and on a diet which by conventional criteria is itself
deficient in protein (4). Furthermore, there is no relationship between the rate of
loss of edema and the dietary protein intake (4). At present the cause of nutritional
edema is unknown. Several of the other cardinal features of malnutrition, such as
dermatosis, hair discoloration, and fatty liver, are unexplained: They are not seen
in experimental animals malnourished with formula diets containing a sufficient
vitamin and trace element supplement; they are seen in animals given the foods
ingested by malnourished populations. The other features of malnutrition, such as
anorexia, diarrhea, wasting, stunting, and hypoalbuminemia, are common to many
noxa apart from protein and energy deficiencies. It is quite possible that trace
element deficiencies singly or in combination play a primary role in the genesis of
some of the features of malnutrition.

GENERAL CONSIDERATIONS

Although it is the purpose of this chapter to examine the part played by trace
elements in malnutrition, we must never lose sight of the fact that these substances
fit into a much larger and complex situation. We will not progress if we simply
debunk one nutrient as being responsible and then search for another candidate to
take its place. It is just as naive to lay everything at the feet of zinc, for example,
as it is to bow down to the dogma of protein deficiency. There is evidence for
deranged metabolism of almost all the trace elements in malnourished individuals.
Understanding the detailed mechanisms of these changes is likely to bear more fruit
than searching for a therapeutic panacea. In malnutrition the changes result from
both the noxa themselves and the physiological adaptations to these events; indeed, no
system has yet been studied in the malnourished child and found to be normal
(5). The abnormalities described in trace element nutrition must be viewed in this
context.

Two questions must be asked with each trace element. First, what role is an
inadequate intake of this element playing in the genesis of malnutrition and the
various manifestations of the illness? Second, what effects have the altered body
composition, physiological responses, metabolic aberrations, and pathological se-
quelea on the trace element’s metabolism?

TISSUE CONCENTRATIONS

There are surprisingly few data on the gross tissue concentrations of trace
elements in malnutrition, and those there are use outmoded analytical techniques.
The data of Cheek et al. (6) and Warren et al. (7) are shown in Fig. 1, along with
data for electrolytes and protein. On the left are shown the concentrations in muscle
and liver biopsies taken from malnourished children. These are compared with
either control individuals or recovered individuals. It is important to point out that
anthropometric recovery in weight-for-height does not ensure a return to a normal
body composition (11,12). It is immediately obvious that all the components of
liver and muscle tissue are reduced to about the same extent. The units used for
The tissue concentrations of protein, RNA, and metals in malnourished and control children. Results are given as follows. Liver: zinc, copper, manganese—mmol/kg fat-free dry tissue (7). Muscle: zinc—mmol/kg fat-free wet tissue; magnesium—10^-1 x mmol/kg fat-free wet tissue; RNA—g/g DNA (6); potassium—10^2 x mmol/kg fat-free wet tissue (8). Head: potassium—10^2 x mmol/whole head (9). Whole body: soluble protein (noncollagen protein)—g/g total protein (10).

FIG. 1. Tissue concentrations of protein, RNA, and metals in malnourished and control children. Results are given as follows. Liver: zinc, copper, manganese—mmol/kg fat-free dry tissue (7). Muscle: zinc—mmol/kg fat-free wet tissue; magnesium—10^-1 x mmol/kg fat-free wet tissue; RNA—g/g DNA (6); potassium—10^2 x mmol/kg fat-free wet tissue (8). Head: potassium—10^2 x mmol/whole head (9). Whole body: soluble protein (noncollagen protein)—g/g total protein (10).

The variables in Fig. 1 are the authors’ original gravimetric reference measurements (per gram fat-free wet weight or fat-free dry weight). As the water/solids ratios for liver (13) and muscle (14) are about the same in malnourished and control/recovered children, the results are comparable. They show a general reduction in the trace metal content per unit tissue. However, the reduction in electrolyte, RNA, and soluble protein is approximately of the same proportion as that of the trace metals. There are difficulties in using dry solids (or wet weight) as the reference measurement for these variables. About 30% of hepatic dry weight, after an overnight fast, in a malnourished child is glycogen (13), an extremely variable component of fat-free dry solids. The proportion of collagen to noncollagen tissue in muscle is much higher in malnutrition (6,9), and, again, muscle glycogen makes a variable contribution.

In Fig. 2 are plotted the same data. However, in this case they are expressed per unit DNA using conversion factors derived from Waterlow and Weisz (13) for liver. There are obvious difficulties in using a conversion factor for postmortem samples from African children that was derived from liver biopsies of Jamaican infants. Nevertheless, it is again apparent that all cytoplasmic constituents are reduced to about the same extent in malnourished individuals in both liver and muscle. Obviously, finding a low tissue concentration (depletion) of any one component cannot
be confidently ascribed to its "deficiency," and one is, of course, not justified to conclude that any pathological correlates are caused by this deficiency.

The trace elements are, for the most part, locked into soluble enzyme proteins: their fate and the capacity of the tissue to retain the metal is inextricably linked to that of the protein. The tissue level may be low because the enzyme is not required, except at a low specific activity, or because the enzyme cannot be synthesized. If the former then it is likely that most soluble proteins will be dispensed with, whereas with the latter there could be a disproportionate reduction in those metalloenzymes dependent on that specific metal's availability. In Fig. 3, the data have again been transformed using conversion factors for soluble protein derived from Jamaican tissues (13) and Cheek's original reference with allowance for collagen protein (15). Given the nature of the assumptions in these transformations and the uncertainties of the correction factors, there is remarkable agreement between the values for malnourished and control tissues. These data serve to demonstrate the difficulties in the interpretation of gross tissue contents of trace elements, particularly when there are differential changes in the components of the tissues directly caused by the pathological process being investigated. Choice of the correct reference measurement to express the data is crucial; it is frighteningly easy to reach the wrong conclusions from limited data and an inappropriate (but easily measured) reference point.

In brain and its constituent parts, whose composition is largely preserved in the malnourished child, no differences have been found in copper, zinc, or manganese concentrations between malnourished and control children (16).

**ZINC**

**Effect of Malnutrition on Zinc**

Low concentrations of zinc have been reported in liver (7), muscle (6), and plasma (17) of malnourished children. However, there is not a disproportionate
reduction in tissue zinc. The reason for the decrease is almost certainly secondary to the reduced metabolic activity and protein turnover of muscle and liver. This conclusion is in keeping with the rapid fall in liver zinc in acute hepatitis (18) and muscle zinc when an imbalanced amino acid mixture is fed (N. T. Davies, personal communication). It is also in keeping with the enigmatic experimental finding that a zinc-deficient diet itself does not lead to a lowered gross tissue zinc concentration.

A number of authors have advocated the use of white blood cell (WBC) zinc concentration to assess zinc nutritional status (19). As WBC zinc correlates with other tissue zinc concentrations (20), these measurements may tell us about the general nutritional status of the animal but, almost certainly, tell us nothing about the zinc status. Indeed in keeping with this interpretation, Aggett et al. failed to demonstrate a fall in WBC zinc in zinc-deficient swine (21).

We can conclude from these considerations only that malnutrition affects zinc metabolism, rather than vice versa, and measurements such as decay curves of injected (or absorbed) radiozinc will be consequently uninterpretable in terms of zinc nutriture.

**Effect of Zinc on Malnutrition**

What of the role of an inadequate intake on the genesis of malnutrition? There are striking clinical similarities between malnutrition and acrodermatitis enteropathica (AE): They both show anorexia, diarrhea, skin excoriation and breakdown, immunoincompetence with fungal infections, and an altered affect. Furthermore, the circulating zinc levels frequently approach those seen in AE. A priori, it is tempting to speculate that actual zinc deficiency has some effect on the expression
of malnutrition apart from the alterations in zinc metabolism occasioned by the other components of the condition.

Malnourished children present with spectra of clinical signs. We therefore examined plasma zinc concentration in relation to the various clinical features of malnutrition (17). There was no relationship with a history of acute or chronic diarrhea, observed stool frequency after admission to the ward, or anorexia. There were statistically independent relationships between plasma zinc and nutritional edema, skin ulceration, and stunting in height. These relationships do not, of course, demonstrate cause and effect. Although plasma zinc concentration is probably the best biochemical indicator of zinc status currently available, zinc deficiency can be demonstrated only by observing the effects of supplementation under specific conditions and with appropriate controls.

To determine if nutritional edema was related to zinc deficiency, edematous children were either given a maintenance diet supplying 1.5 μmol zinc/kg/day (0.1 mg) or were supplemented with 30 μmol zinc/kg/day (2 mg). There was no difference in the rate at which edema was lost between the two groups. Indeed, the basal diet itself could be considered zinc-deficient: The children lost their edema rapidly and consistently despite being on this diet. The low plasma zinc level seen in association with edema is thus probably secondary to the underlying pathology; there is no reason to believe that zinc deficiency is in any way causatively associated with nutritional edema.

One of the major problems in studying the malnourished child is finding the appropriate control. The complexity and heterogeneity necessitate either very large series of carefully matched individuals or the use of the children as their own controls. Unfortunately, during the first few days after admission the clinical changes in the children are rapid. Their infections are treated, diarrhea controlled, and major electrolyte imbalances corrected. They have a remarkable improvement in affect, and they lose their edema. Large supplements of potassium, magnesium, and vitamins are given therapeutically.

Over this time of rapid metabolic change it is very difficult to ascribe any measured change to provision of a particular nutrient despite the correlation which often exists, unless the response is dramatic and consistently fails to occur when that specific nutrient alone is withheld from the therapeutic regimen.

When examining the relationship between zinc and the skin lesions of malnutrition, we circumvented this problem of control by specifically selecting children with symmetrical skin lesions on their limbs. In this way one side of the child could act as control, and the other was treated with local zinc. Any change in the general condition of the child thus affected each side identically. A double-blind sequential trial showed much more rapid healing of the sores with zinc supplementation (22). Since that time, zinc has been routinely prescribed for children with open skin lesions: They heal rapidly and completely, and we no longer encounter lesions that become indolent, as in the past. We can probably ascribe these lesions, which are very similar to those found in AE, to zinc deficiency.
The interesting association between stunting and low plasma levels may well be due to chronic mild zinc deficiency, similar to that described by Hambidge's group in Denver (23). Because the children do not receive the same diets after returning home as they received while developing malnutrition, this hypothesis is not as easily amenable to experimental verification as it was in Denver.

Another cardinal feature common to both AE and malnutrition is increased susceptibility to infection. Again, when assessing the immune status of these children the results are likely to be confounded by the clinical changes that occur after admission. We therefore used the same technique of topical application of zinc and placebo ointments to increase the local cutaneous zinc concentration at the site of testing for delayed cutaneous hypersensitivity (24). We used the ubiquitous Candida antigen to which all the children had been naturally exposed. The results of this study showed that all the tests in the zinc-supplemented arm gave positive reactions, whereas on the unsupplemented side some children gave normal reactions and some hardly reacted at all. The children with the most depressed responses on the unsupplemented arm had the lowest plasma zinc concentrations. This result indicates that much of the susceptibility to infection in malnutrition may be attributable to inadequate supplies of zinc.

However, in further studies in malnourished infants and some malnourished adults (postgastrectomy), we have identified several individuals whose reactions are inhibited by topical zinc (25). It is likely that in these individuals some other nutrient, which is antagonized by zinc, is limiting the delayed hypersensitivity response. Alternatively, these individuals may achieve such high local zinc concentrations that they become inhibitory.

As with vitamin A-associated xerophthalmia, all the children do not have skin lesions or such infections as candidiasis. Severe zinc deficiency does not seem to be central to the genesis of malnutrition (either marasmus or kwashiorkor), but it often complicates malnutrition. It can be recognized clinically by the skin lesions and mucosal candidiasis, and appropriate supplements can be given.

Zinc Nutriture During Recovery

We cannot conclude from Figs. 1 and 2 that zinc deficiency per se occurs in malnutrition; however, it is obvious that to return the muscle and liver to normal will require additional zinc, as well as all the other protoplasmic constituents. On an individual cell basis (DNA) the content of zinc is less than half that of a normal cell in both liver and muscle. These tissues, particularly muscle, form the major components of body weight. Mixed muscle tissue contains about 1.7 \( \mu \text{mol Zn/g wet weight} \) (26). If the body is about one-third muscle tissue and the concentration of zinc in muscle has to be doubled to allow for repletion of its full normal activity, there will need to be a retention of \( 1.7 \times 300 \times 0.5 = 255 \ \mu \text{mol zinc/kg body weight} \). Thus just to return existing muscle tissue to its normal state (per DNA which infers hypertrophy) will require a retention of 255 \( \mu \text{mol (16.6 mg) zinc/kg} \). For a 5-kg child this represents the total recommended dietary allowance for more
than 2 weeks. When we consider that no account has been taken of the repletion requirements for other tissues or of the facts that zinc is not 100% utilized and there are continuing losses, it is obvious that large quantities of zinc will be required during rehabilitation if the metabolic adaptations are to be successfully reversed. To this must be added the requirement of zinc for new tissue synthesis.

Typically, a recovering malnourished child may gain weight at a rate of 15 g/kg/day. If this were lean tissue with a zinc content similar to normal mixed muscle, a 5-kg child would need to retain an additional 127 μmol (8 mg) zinc/day. Of course, if half the weight gained was fatty tissue, only half this amount would be required; nevertheless, it then represents nearly the total recommended daily allowance, again with no allowance for continuing losses or incomplete absorption.

It is obvious that during rehabilitation very large amounts of zinc are required to replete depleted tissues and to permit growth. None of the currently used diets supply anywhere approaching the amounts of zinc required to return the child to normal. It is perhaps for these reasons that anthropometrically recovered children still have thin atrophic muscle fibers (11) with a much reduced zinc concentration (6).

Malnourished children who are given maintenance diets, which do not permit growth and supply only 1.5 μmol zinc/kg/day (less than the content of 1 g of muscle), maintain their plasma zinc concentration (26). When they are given an increased diet so that they can gain weight rapidly, even provision of the recommended dietary allowance does not prevent a profound fall in the plasma zinc concentration. This remains low throughout recovery and returns to normal only when the children cease gaining weight rapidly. There is a direct relationship between the fall in plasma zinc and the rate of weight gain, emphasizing the dominant role growth has on zinc requirements (26).

Although zinc deficiency may not be a feature of malnutrition on presentation, failure to provide sufficient zinc may well limit the rate of growth and give rise to a conditioned zinc deficiency.

To test whether zinc deficiency does in fact supervene during recovery from malnutrition, we have supplemented children with zinc in the later stages of rehabilitation. There is a dramatic and immediate increase in the rate of weight gain (27). Accompanying this is a decreased energy cost of growth, from over 60 kJ/g weight gained to about 30 kJ/g weight gained. We interpret this to mean that more lean tissue is being synthesized with the provision of zinc, in accordance with the isotopic measurements of changes in muscle mass that have been made in similar children (28).

It is important to emphasize that zinc is only one of the constituents of protoplasm. If any one other constituent is not supplied in adequate amounts, there is a similar limitation on growth and conditioned deficiency. Zinc is very unlikely to be unique in this regard.

That these children are indeed zinc-deficient after recovery is demonstrated by the growth of their thymus gland with zinc supplementation (29) and stimulation of their WBC sodium pump activity (30), as well as their growth responses. These
children did not display the overt clinical signs of dermatosis, diarrhea, or anorexia classically associated with severe experimental zinc deficiency.

That these signs are displayed only by children with severe zinc deficiency is illustrated by the case of one subject who grew very rapidly on a phytate-containing soya formula. The child's plasma zinc concentration fell to 3.5 μmol/liter (23 μg/dl) and remained at that level for several weeks. The child then developed mild diarrhea and a minimal skin rash on his upper lip and anus. He was given a single dose of 92 μmol (6 mg) zinc, equivalent to 15 μmol (1 mg)/kg body weight. Within 1 day the lesions had healed and the diarrhea stopped. There was no change in his plasma zinc level, which remained at 3.5 μmol/liter. Following this single dose the child completed a metabolic balance study without any recurrence of symptoms or signs.

When a child presents with zinc-responsive skin lesions and diarrhea he is analogous to the iron-deficient child presenting with koilonychia and a cricoid web. Mild zinc deficiency can cause abnormalities of immune function, electrolyte homeostasis, body composition, and growth without dramatic or even overt clinical signs. The responses to supplementation in humans (27) and experimental animals (31) are extremely rapid, being measured in hours or at most days; this means that a therapeutic trial of zinc supplementation is a practicable test of zinc deficiency. However, we are as yet unsure of the most sensitive physiological or biochemical variable to monitor for a response: It is likely to be some aspect of T-cell function, as these cells seem to be particularly sensitive to zinc deficiency.

COPPER

Effect of Malnutrition on Copper

The liver copper concentration, on a dry-weight or DNA basis, is reduced in African children with edematous malnutrition (32). However, as with zinc, the degree of lowering is in keeping with the reduction in soluble protein. It is thus unlikely that there is a specific deficiency of total copper; in other words, the deficit is not out of proportion to the other components of hepatic protoplasm.

In contrast to the findings reported in edematous malnutrition, the same workers reported a slightly elevated (nonsignificant) copper concentration in the livers of children who died from marasmus, again on a dry-weight basis (33). If the arguments about reference measurements are valid, we would have expected a fall in copper concentration in marasmus. Thus although the elevated copper concentration reported may not be statistically significant, it may be biologically significant. One of the characteristic differences between kwashiorkor and marasmus is that kwashiorkor has a reduction in the circulating levels of hepatic export proteins; most notable is albumin, but transferrin, retinol-binding protein, prealbumin, thyroxine-binding protein, and several others are reduced. In marasmus these proteins tend to be better preserved (there is a considerable overlap in the observed ranges). Fatty liver and disturbed liver function tests, although they do occur in marasmus,
are much more common in kwashiorkor. It is likely that the pathological and metabolic differences between the two major forms of malnutrition account for the difference in hepatic copper content.

In 1971 the same African group reported copper concentrations in brain, heart, muscle, and skin from patients with marasmus, marasmic kwashiorkor, and kwashiorkor (16). In confirmation of their previous reports, kwashiorkor children had low copper levels in their livers; copper was also reduced in heart and skeletal muscle. In this series there were slight reductions in these same tissues in marasmus (Table 1). However, the results from the children with marasmic kwashiorkor, an intermediate form of severe malnutrition, had grossly elevated mean concentrations of copper in liver, muscle, and heart. The authors offer no explanation for this finding.

Skin copper was high in all forms of malnutrition. As there is marked dermal atrophy in malnutrition, it is likely that the composition of this highly compartmentalized tissue was altered sufficiently to render interpretation of gross skin copper concentrations impossible with a gravimetric reference.

Whatever the cause of the high copper values in some of these children's tissues, it seems safe to conclude that South African children with malnutrition are unlikely to be copper-deficient. Unlike zinc, hepatic copper concentration is responsive to copper deficiency (and toxicity) in experimental animals. Unfortunately, we do not have reports of tissue copper levels from other parts of the world to determine if these results are peculiar to South Africa or are general.

Table 2 shows the plasma/serum copper values in malnourished children. It is clear that mean circulating copper is consistently reduced in patients with kwashiorkor. In marasmic children the reduction in plasma copper is much less. These values are, of course, mean values; examination of all the series shows that, within each group, there are very much wider ranges of copper concentration, with many individual children having values below and above the control ranges.

What do these measurements mean? The vast majority of circulating copper is in a glycoprotein, ceruloplasmin, which functions as a ferroxidase. There is con-

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Copper (μmol/g dry tissue)</th>
<th>Marasmus</th>
<th>Kwashiorkor</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>1.68</td>
<td>8.06</td>
<td>0.76</td>
<td>2.19</td>
</tr>
<tr>
<td>Heart</td>
<td>1.81</td>
<td>2.86</td>
<td>1.51</td>
<td>2.27</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.08</td>
<td>1.67</td>
<td>0.54</td>
<td>1.29</td>
</tr>
<tr>
<td>Skin</td>
<td>1.05</td>
<td>1.62</td>
<td>0.57</td>
<td>0.40</td>
</tr>
<tr>
<td>Cerebral gray matter</td>
<td>2.06</td>
<td>1.90</td>
<td>2.30</td>
<td>2.54</td>
</tr>
<tr>
<td>Cerebral white matter</td>
<td>1.31</td>
<td>1.56</td>
<td>1.02</td>
<td>1.35</td>
</tr>
</tbody>
</table>

From Lehmann et al. (16).
TABLE 2. Plasma/serum copper concentrations in malnourished children*

<table>
<thead>
<tr>
<th>Country</th>
<th>Date</th>
<th>K</th>
<th>M</th>
<th>C</th>
<th>K/C (%)</th>
<th>M/C (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chile</td>
<td>1962</td>
<td>—</td>
<td>10.1</td>
<td>14.1</td>
<td>—</td>
<td>72</td>
<td>34</td>
</tr>
<tr>
<td>Peru</td>
<td>1983</td>
<td>—</td>
<td>21.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>35</td>
</tr>
<tr>
<td>Jamaica</td>
<td>1966</td>
<td>—</td>
<td>5 of 11, &lt;14.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>36</td>
</tr>
<tr>
<td>Egypt</td>
<td>1974</td>
<td>11.7</td>
<td>13.5</td>
<td>14.9</td>
<td>78</td>
<td>91</td>
<td>38</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1960</td>
<td>13.7</td>
<td>—</td>
<td>28.6</td>
<td>48</td>
<td>—</td>
<td>39</td>
</tr>
<tr>
<td>S. Africa</td>
<td>1974</td>
<td>15.7</td>
<td>—</td>
<td>39.5</td>
<td>40</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>India</td>
<td>1963</td>
<td>8.9</td>
<td>22.5</td>
<td>18.9</td>
<td>47</td>
<td>119</td>
<td>41</td>
</tr>
<tr>
<td>Pakistan</td>
<td>1978</td>
<td>20.3</td>
<td>20.8</td>
<td>22.9</td>
<td>89</td>
<td>91</td>
<td>42</td>
</tr>
</tbody>
</table>

*K, kwashiorkor; M, marasmus; C, control.

TABLE 3. Effect of infection on serum copper levels in children with kwashiorkor

<table>
<thead>
<tr>
<th>Not infected</th>
<th>Chronic</th>
<th>Fever</th>
<th>Control</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.9</td>
<td>20.2</td>
<td>—</td>
<td>18.9</td>
<td>41</td>
</tr>
<tr>
<td>14.8</td>
<td>28.7</td>
<td>25.6</td>
<td>22.8</td>
<td>42</td>
</tr>
</tbody>
</table>

sequently a close relationship between the concentration of ceruloplasmin and total copper in the plasma. Ceruloplasmin is, like albumin and the other proteins cited, a hepatic export protein. Low circulating levels are therefore to be expected in conditions such as kwashiorkor where there is reduced synthesis and release of hepatic export proteins. However, unlike the other proteins, ceruloplasmin is an acute-phase reactant, secreted in large amounts by the liver in response to inflammatory stress. This complicates the interpretation of circulating copper. Comparison of the plasma copper concentration from children without an overt infection with those who have a chronic infection such as tuberculosis or even simply a fever (Table 3) shows that, even in kwashiorkor, the liver can secrete sufficient ceruloplasmin in response to an infection to elevate the circulating copper concentration.

Variations in the degree of hepatic dysfunction, the types and severity of infections, and the ability of the body to synthesize the mediators of the inflammatory response are the major determinants of circulating copper levels. They cannot be interpreted, with any precision, in terms of copper nutritional status.

Effect of Copper on Malnutrition

In order to assess the effect of copper on the genesis and features of malnutrition it is necessary to have a reliable measure of copper status which will not itself
simply reflect the occurrence of other pathogenic processes. Such a measure has not been established with certainty. We have been exploring the use of the red blood cell (RBC) enzyme copper/zinc superoxide dismutase (CuSODA). In rats the activity of CuSODA is responsive to dietary manipulations of copper and is totally unresponsive to manipulation of dietary zinc (43).

We have confirmed this observation in children. Twenty-five recovering children were given a milk-based diet ad libitum which supplied between 1 and 2 μmol Cu/kg body weight/day depending on the total intake. They were compared with 25 children who were given a supplement of 3.2 μmol Cu/kg/day. Over a 5-week period the CuSODA of the unsupplemented children fell from 2,852 ± 193 to 2,156 ± 184 U/g Hb; this represents a fall of 0.7% per day or 70% over the life span of the RBC mass (100 days). In the children receiving the supplement the CuSODA rose slightly from 2,813 ± 137 to 2,956 ± 143 U/g Hb. Thus CuSODA is responsive to dietary copper intake in humans. However, we have still not sufficiently explored the specificity of this response. From consideration of animal studies, the constancy of this enzyme’s activity across species, and the fact that superoxide, the enzyme substrate, readily induces the manganese form of the enzyme rather than the copper zinc protein, it seems improbable that CuSODA is sensitive to other noxa. Nevertheless, conclusions drawn from CuSODA should be interpreted with caution particularly in those diseases which affect the formation and maturation of RBCs.

On the other hand, CuSODA has several distinct advantages. Being an RBC enzyme, its activity reflects the body’s copper status at the time the cell was formed. This means that the activity gives an integral of the copper status over a period of about 15 weeks; it also allows us to look back in time at the copper status of the child while his illness was developing. It should be totally insensitive to acute infections and is unlikely to be specifically affected by hepatic pathology.

Red blood cell CuSODA was measured in 93 severely malnourished children: 25%, 9%, and 3% had values more than 2, 3, and 4 SD, respectively, below those of the control group. None of the children had high values. Unlike the plasma total copper and tissue copper concentrations, there was no difference between the values from children with kwashiorkor, marasmic kwashiorkor, and marasmus (Table 4). Furthermore, there was no relationship between CuSODA and any particular clinical feature on admission; in particular, hepatomegaly, skin lesions, dyspigmentation, hair changes, anemia, and leukopenia did not relate to CuSODA. Of even greater importance, there was no relationship between the values of the children who lived and those who died.

We tentatively draw the conclusion that copper deficiency occurs in a relatively small percentage of Jamaican children with severe malnutrition (about 12%). It seems unlikely that any of the major features of malnutrition are secondary to copper deficiency, although this aspect has not been properly, or fully, explored.

Copper Nutriture During Recovery

Cow’s milk and the infant feeding formulas derived from cow’s milk have been used fairly successfully to treat severe malnutrition throughout the world. Cow’s
milk is particularly poor in copper and indeed forms the basis of the experimental diets used to induce copper deficiency in animals. The rapid recovery of the signs of malnutrition on a milk-based diet emphasizes that copper deficiency is unlikely to be responsible for any of these signs. Given the usual initial body depletion of copper (on a DNA basis) and the added nutritional requirements for greatly increased rates of weight gain, recovery from malnutrition on a milk-based formula will almost inevitably give rise to copper deficiency. That this happens in nearly every case is demonstrated by our observation of a fall in CuSODA level in the 25 unsupplemented children who had measurements made. We did not observe any overt clinical signs which could be ascribed to copper deficiency, but detailed physiological measurements were not undertaken.

Cordano et al. in two reports (36,45) described 19 infants who developed overt signs of copper deficiency during recovery from marasmus. These scientists maintained their infants on these diets, in hospital, for very long periods of time (typically 6 to 9 months), whereas our infants were on recovery diets for 18 to 62 days (mean 33 days). Thus a difference in scale of deficiency probably accounts for the lack of overt signs in our infants. Cordano’s group described progression of osteopenic bone changes to the stage of pathological fractures (45). Their infants developed anemia and neutropenia.

Castillo-Duran et al. (35) conducted a controlled trial of copper supplementation in recovering marasmic children in Chile. They found no difference in the prevalence of anemia, leukopenia, or rates of weight gain in the two groups after 60 days. However, they reported that their unsupplemented children had a higher prevalence of severe lower respiratory tract infection, although fever and all infective episodes were not different between groups.

At present it seems that all children given an unsupplemented milk-based diet during recovery will develop biochemical evidence of copper deficiency. What, if any, deleterious effects this has over a time course of up to 2 months is at present unclear.
SELENIUM

There are no data on the tissue contents of selenium in children with malnutrition. We are not in a position to assess what effect malnutrition itself has on the metabolism of, or requirements for, selenium. By analogy with zinc and copper, we must be cautious when tempted to ascribe causal relationships to observed abnormalities.

Only one report of selenium deficiency in primates was available a decade ago: Muth et al. (46) gave seven squirrel monkeys a low selenium ration for 9 months until one died. By this time their hair was sparse, and they had lost weight. Three animals were then supplemented and fully recovered; three were killed. At post-mortem the animals had hepatic necrosis, cardiac and skeletal muscle degeneration, and nephrosis. These findings bear a resemblance to those found in children dying of malnutrition, and the particular signs displayed by the animals are all of unknown causation in the human disease.

In kwashiorkor the plasma and RBC selenium concentrations are reduced to about half normal in Central America (47) and Thailand (48). These lowered levels may or may not represent a true deficiency. There are two observations which would favor the interpretation of selenium deficiency. First, Burk et al. (47) found that when they incubated RBCs from malnourished children with Na$_2$SeO$_3$, the cells took up and retained twice as much radioselenium as the cells from the control children.

Second, Waterlow et al. (49) attempted to measure whole-body protein turnover in malnourished children using $^{75}$Se-selenomethionine as the tracer amino acid. They compared its metabolism with that of $^{15}$N-glycine. Many metabolic studies have been done with $^{15}$N-glycine, which is thought to be representative of amino nitrogen metabolism. The experiments were a failure for the purpose for which they were designed because the selenomethionine was almost completely retained. Only a small proportion of the administered dose appeared in either urine or feces. Furthermore, in contrast to the expected behavior of an amino acid and the findings with selenomethionine in malnourished rats, when the dietary protein was reduced there was less retention of the radioselenium (Table 5). The most satisfactory explanation for this anomaly is that the selenomethionine was being predominantly

<table>
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<th>Parameter</th>
<th>High-protein diet</th>
<th>Low-protein diet</th>
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<tr>
<td>Specific activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{75}$Se</td>
<td>5.3</td>
<td>7.3</td>
</tr>
<tr>
<td>$^{15}$N</td>
<td>47.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Percent of dose excreted in urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{75}$Se</td>
<td>2.5</td>
<td>4.2</td>
</tr>
<tr>
<td>$^{15}$N</td>
<td>20.0</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*From Waterlow et al. (49).*
affected by the child's demands for selenium and was not following amino acid metabolism. If this is so, the malnourished children indeed have avid retention of selenium.

The selenoenzyme glutathione peroxidase (GPX) catalyzes the removal of hydroperoxides formed from fatty acids during free-radical damage. It thus has a broad role in protecting tissues from oxidative damage (50). This observation explained the interaction between selenium and vitamin E. After identification of GPX as a selenoenzyme, it was quickly shown that the activity of GPX in RBCs is quantitatively responsive to the dietary selenium content (51). Thus an important and vulnerable selenium pool had been identified so that meaningful investigations into the role of selenium in malnutrition could be made.

We have therefore assayed GPX activity in the RBCs of 58 severely malnourished children (52). Twenty-six (45%) had values below the control range (20–57 IU/g Hb). There was no difference in the proportion of low values in patients with kwashiorkor, marasmic kwashiorkor, or marasmus. There is no relationship between GPX activity and the presence or absence of edema.

There was, however, a relationship between the presence and degree of hepatomegaly and low GPX activity. There was also a relationship between depressed levels of GPX and increases in plasma levels of hepatic enzymes, particularly aspartate aminotransferase. These results are particularly intriguing as the RBC enzyme should represent the selenium status over the period that the child was developing severe malnutrition, whereas the liver pathology represents the immediate condition.

The ultimate measure of severity is death: There were six patients who died in this series; five had GPX activities below normal. All those who died had grossly fatty livers at postmortem.

Many of the children die from cardiopulmonary distress. Within a few days of admission they develop acute dyspnea, cyanosis, pulmonary crepitations, cold peripheries, a weak pulse, gallop rhythm, and engorged neck veins. All except one of the 11 patients who developed this condition had GPX levels at or below the lower limit of normal. Indeed almost half the patients with low GPX activities suffered this complication. Four of the children died from this cardiopulmonary syndrome. At death they all had grossly dilated ventricles as well as fatty livers.

There is a marked similarity between the signs displayed by animals who die from experimental selenium deficiency and these children who died from malnutrition. The finding of a low GPX value in these children may well be more than an epiphenomenon.

During recovery the RBC GPX level does not change substantially on our currently used diets. There is no relationship between the GPX values, either on admission or subsequently, and the rate of weight gain of our children.

IRON

Anemia is almost universal in malnourished children. It is most frequently hypochromic and microcytic. As serum iron has been repeatedly shown to be low
(53), the anemia has been assumed to be due to iron deficiency. Therapeutic iron supplements consequently form part of almost every treatment regimen.

Indian reports, however, suggested that children with kwashiorkor have high circulating ferritin values (54). A crude biological assay, inhibited by antiferritin antibodies, was used for this pioneering work. The crudity of the assay and the suggested hypothesis that free ferritin in plasma was antidiuretic and therefore the direct cause of nutritional edema led to skepticism about the results in some quarters. Others believed that these high ferritin levels must be peculiar to India, and the results were generally discounted as being relevant to the disease as seen elsewhere.

With the evidence of sensitive immunosorbent assays for ferritin, it is possible to reexamine the role of ferritin in malnutrition. This is particularly relevant, as circulating ferritin is in equilibrium with iron stores and can give an indication of the body burden of iron.

We have consequently measured admission ferritin concentrations in 163 children with severe malnutrition. The levels were well above the control pediatric range and close to the normal adult range. There was no difference between the edematous and nonedematous children. We therefore failed to substantiate Srikantia’s hypothesis that circulating ferritin was the cause of edema (54).

Of great interest, however, is the observation that all the children who died had very high (>250 μg/liter) plasma ferritin values. Figure 4 shows the relationship between admission ferritin levels and mortality rate. Clearly plasma ferritin is an excellent prognostic indicator. The question arises as to whether this represents ferritin which has gained access to the circulation by liver damage or it is truly representative of increased iron stores in malnutrition. Concurrent measurement of liver-derived enzymes shows no good correlation with plasma ferritin. Furthermore,
measurement of the values at discharge show that the high ferritin concentrations are maintained. These observations tend to support the proposition of a high body burden of iron in malnutrition in Jamaica.

There have been few recent reports of tissue iron in kwashiorkor. Waterlow, in an early study, demonstrated that children who died of malnutrition had high levels of hepatic iron (55). Malnourished children had $27.6 \pm 4.7 \mu$mol/g fat-free dry weight ($N = 14$), whereas the normal values lie in the range 3.5 to 12.5 $\mu$mol/g. Waterlow was able to quote several earlier papers which supported and generalized his findings. In his report he made a very germane comment:

There was satisfactory correlation with the histological findings, so that it was possible by examination of the section to obtain a fairly accurate idea of the amount of iron in the liver. However, in none of the biopsy specimens of the liver was iron demonstrated histologically. It is difficult to understand why iron should be present in the liver in fatal cases and absent in babies, who were clinically similar, but did not die.

This observation fits precisely with our ferritin results obtained 38 years later and leads us to the conclusion that body burdens of iron are indeed often high in malnutrition.

Although Waterlow ascribed the differences he found to postmortem chemical changes in staining characteristics, it seems probable that high levels of hepatic iron are indeed associated with mortality. During the time since Waterlow made this observation, much has been learned about iron biochemistry: It is no longer improbable that iron accumulation could cause death.

Iron is one of the major biological generators of free-radicals, particularly the highly damaging hydroxyl radical. The association of low selenium status, which through reduced activity of glutathione peroxidase results in inadequate protection from lipid peroxidation, a low level of vitamin E (56), and high levels of storage iron, may result in fatal generation of free-radicals with unsuppressed chain reactions of lipid peroxidation. It is noteworthy that the children with low GPX activities who survived were those who did not have high plasma ferritin concentrations.

OTHER TRACE ELEMENTS

Molybdenum

There are no direct measurements on molybdenum in malnutrition. However, the molybdenum metalloenzyme xanthine oxidase in liver biopsy specimens has a very low activity (2.6 compared to 6.9 $\mu$mol/g protein/hr) (57). A reduction of this magnitude is disproportionately great and raises the suspicion of molybdenum deficiency. However, xanthine oxidase produces superoxide radicals during its normal activity; its profound reduction may therefore be secondary to an adaptation to prevent free-radical formation. Alternatively, there may be avid retention of purine residues so that xanthine oxidase is simply not required.
Chromium

Two laboratories have reported improvement in glucose tolerance following inorganic chromium supplementation in malnourished children from Jordan, Nigeria, and Turkey. There must be other causes of the impaired glucose tolerance, as all the infants did not respond and a study from Egypt (58) failed to find any effect. In Turkey some of the infants showed a greater weight gain with chromium supplementation (59).

Others

None of the other trace elements have given rise to clinical observations in humans which would point the way to a possible role in malnutrition. However, it is possible that vanadium (60) and manganese (61) will transpire to be important.

ACKNOWLEDGMENTS

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REFERENCES

DISCUSSION

Dr. Hurley: You started by saying that you thought that malnutrition affected trace elements more than trace elements affected malnutrition. Then you proceeded to show us that zinc deficiency does play a role in malnutrition, and you ended by saying that trace elements were crucial in malnourished children; it seems to me that there is a contradiction here. Would you clarify this?

Dr. Golden: We are dealing with a complex situation, and we must not lose sight of the vicissitudes of intermediary metabolism, body composition, and physiological alterations: No physiological measurement has ever been made on a malnourished child and been found to be normal. The malnourished child has adapted over many months to an inadequate intake of energy and many other nutrients. One response to this is a lower RNA level and a low protein synthesis rate. If you are not making protein, what is the point in having thymidine kinase? What is the point in having DNA replicase if you are not dividing cells? These enzymes are dispensed with because they are expensive to make, keep, and maintain. If you do not have these zinc metalloenzymes for good metabolic reasons, you are not going to keep the zinc in the tissue that is in that enzyme. We do not know which is the cart and which is the horse, except by some type of supplementation study. We did this with edema and zinc and found absolutely no difference; the only features on admission which showed that zinc had a probable cause-and-effect relationship was with the skin lesions and maybe with immunocompetence. However, the children who were not immunocompetent and who...
do not have skin lesions did not seem to have functional zinc deficiency even though they are grossly zinc-depleted.

**Dr. Prasad:** In our experience in Egypt, all kwashiorkor patients suffered from panmalnutrition and not only protein-calorie malnutrition. I was not convinced from your presentation that there was any correlation between superoxide dismutase and copper. Do you have any data which show a correlation?

**Dr. Golden:** The children who were supplemented with 3.2 µmol Cu/kg, in addition to dietary copper, had 4 to 5 µmol/kg. The other group had 1 to 2 µmol/kg. In other words, one group had three times the intake of copper than the other group had. The ones who had the higher copper intake did not have a decrease in their superoxide dismutase. In the children who did not have copper, the superoxide dismutase fell. Those are two groups of children: one without and one with copper supplementation. Without copper the SOD fell, with it it did not fall.

**Dr. Prasad:** I agree with what you said with respect to ferritin. I am wondering if serum folate and B₁₂ were deficient because this would then give high ferritin levels.

**Dr. Golden:** Some of the children had folate deficiency, some had sickle cell anemia, and a number had acanthocytosis. A number had hemolytic anemia for which we could not find any obvious cause except for the fact that the vitamin E levels were a bit low; some of them had just ordinary normocytes, and many had target cells. What the actual cause of the anemia is, one is not sure; Viteri has published data showing that there is a relationship between the total circulating hemoglobin in malnutrition and the metabolic rate; these children had a low metabolic rate and anemia. What he was suggesting is that the "anemia" is often a functional anemia: they do not require that much oxygen-carrying capacity with the very low oxygen consumption of their tissues, and therefore when they break down a red cell they do not replace it and the iron goes into storage. It is only when their metabolic rate goes up that they resynthesize their hemoglobin. Therefore the actual cause of the anemia is not clear. Our children are certainly often anemic.

**Dr. Cheek:** It is clear from the information you presented that you are dealing with a reduction of all nutrients, e.g., protein, calories, vitamins, and trace elements. The protein reserves are low, and microscopically you would find a gross reduction in cytoplasmic growth. However, there are different forms of malnutrition. For example, one can produce protein sufficiency and caloric deficiency in rats without any loss of cytoplasmic growth (Durand et al. *Ann Biol Anim Biochem Biophys* 1967;7:145; Hill et al. *Johns Hopkins Med J* 1970:127:146–75). Yet cell replication grinds to a halt. Such rats show imbalances in insulin and growth hormone. Years ago we emphasized that growth hormone activity was more related to energy input and insulin release to protein intake, whereas growth hormone controls the cell number in muscle and insulin cell size (Cheek, Graystone. *Kidney Int* 1978;14:317), a hypothesis that applies equally well to the kidney (Hutson et al. *J Pediatr Surg* 1984;19:24–8). Unlike rats, primates accept a low protein but adequate caloric diet, yet little work has been done in that area. Thus the points of reference become very important and a knowledge of cell growth, size, and number, rate of replication, and protein accretion and degradation become important, yet difficult to document.

**Dr. Golden:** We have great difficulties with reference measurements and are dealing with a very heterogeneous population in terms of cells, cell growth, and cell changes and yet stereotyped in the fact that most of the children have low intakes of many nutrients.

**Dr. Janghorbani:** I want some clarification regarding your reference to retention of selenomethionine. I thought there was an implication that the retention of selenium was high because these children were malnourished. I wanted to bring to your attention what you
probably already know, namely, that there is a great deal of information using both stable and radiotracer type studies that have established that retention of selenium in many forms, including selenomethionine, is generally high.

**Dr. Golden:** I am unaware of any other studies where a second labeled amino acid has been given simultaneously with selenomethionine in order to find the difference between the retention that could be related to incorporation into protein of the selenomethionine and that related to other pathways. Using glycine as a reference point is one of the nice things about Waterlow’s data. Your point is well taken that there is high selenium retention from selenomethionine in many situations.

**Dr. Bergmann:** Dr. Hambidge, you have demonstrated that recovery from malnutrition, i.e., rapid growth, may actually make trace element deficiency appear. I would like to share an observation with you in normal children. We studied longitudinally growth in normal children in whom we had hair samples at the beginning of the study and at the end. We found that even in normal children there was a decrease in hair zinc concentration in relation to the rate of growth. This negative correlation was statistically significant. We believe that normal growth may in part be responsible for changes in what might be called “body reserves” of trace elements.

**Dr. Golden:** Yes, I believe growth is the most important determinant of zinc requirement, particularly in conditions such as convalescence from illness and fever when normal people undergo catch-up weight gain.

**Dr. Bergmann:** We do not believe that hair zinc is a good parameter of individual zinc status. However, for population studies, it may be useful.

**Dr. Gebre Mehdin:** Dr. Golden, I have a comment and a question relating to the doubt you expressed about the relationship between trace elements and soluble proteins, as you referred to them. Here is an example of a child with leukemia, who shows loss in weight and a reduction of hemoglobin, albumin, prealbumin, and several trace elements. When you feed this child with an ordinary diet all the parameters mentioned above become normal. We do not see the discrepancy between trace elements and soluble proteins that you have mentioned. On the contrary, we see here a clear correlation between them. My second comment relates to ferritin. We were rather enthusiastic about the use of ferritin in studying iron status. The problem, of course, is that ferritin is influenced by infections. I think most of your children, when they die, die of sepsis or some kind of subclinical infection, as do our children. What do elevated ferritin levels indicate in your children?

**Dr. Golden:** The question of ferritin and infection is very important, and it was one of the first things we thought about. We must study this area properly, and we have just started. One of the things we are planning to do is to bind ferritin to ELISA antibodies and then measure how much iron has been found to determine whether it is actually iron-containing ferritin or empty ferritin because that may help resolve the very problem you brought up.

**Dr. Goyens:** In Zaire we studied the zinc and copper status of patients with kwashiorkor and marasmic kwashiorkor. We found on admission low serum albumin, low serum zinc, normal serum copper, low superoxide dismutase, low glutathione peroxidase, and low alkaline phosphatase. Despite all these facts, which seem to corroborate your findings, our children behaved very differently from yours when we gave supplements of zinc and copper: The serum zinc levels increased whether we gave zinc supplements, copper and zinc, or copper alone (Table D1). When we did not give any supplement, serum zinc levels did not change during rehabilitation. Thus the response to treatment in our cases differs from that in your children.
TABLE D1. Protein-energy malnutrition in Kivu: effect of zinc and copper supplementation on serum zinc levels

<table>
<thead>
<tr>
<th>Condition</th>
<th>No.</th>
<th>Serum zinc (µg/100 ml)(mean ± SD)</th>
<th></th>
<th>p</th>
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<tr>
<td></td>
<td></td>
<td>On admission</td>
<td>After 45 days*</td>
<td></td>
</tr>
<tr>
<td>1. Nonsupplemented</td>
<td>21</td>
<td>41 ± 19</td>
<td>45 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>2. Plus Cu</td>
<td>28</td>
<td>47 ± 26</td>
<td>71 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3. Plus Zn</td>
<td>29</td>
<td>47 ± 24</td>
<td>63 ± 17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4. Plus Cu and Zn</td>
<td>27</td>
<td>48 ± 23</td>
<td>65 ± 18</td>
<td>&lt;0.001</td>
</tr>
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</table>

#1 versus 3: p < 0.001; 2 versus 3: NS.

Dr. Heresi: In Chile we have the same findings. On admission there is normal serum copper level, but after the infant has achieved a normal weight/length ratio we have a low serum copper level. After supplementation, we achieve normal serum copper and ceruloplasmin levels.

Dr. Golden: The cardiovascular problems occurred within a few days of admission at a time when the children have normal superoxide dismutase levels. With respect to the ceruloplasmin levels, some were very low and some very high, depending on the infective status of the child. I can almost throw back the ferritin and infection question and say that when we measured ceruloplasmin levels on the same bloods, we found that they were low despite the fact that the children had high ferritin levels. The ceruloplasmin does come out in many of the children as an acute-phase reactant at this stage. The recovering and recovered children who have recovered on the milk-based diet are all copper-deficient, with low copper, low ceruloplasmin (unless they have a current infection, in which case their plasma copper will go up again even though they are copper-deficient), and low superoxide dismutase levels.

Dr. Paranjothy: Would the severity of infections be increased by giving zinc and copper to malnourished children?

Dr. Chandra: I doubt it, so long as you stay within a reasonable dosage range. In the case of iron, it may be different. In kwashiorkor children with low transferrin levels, parenteral iron therapy within the first 3 to 5 days of hospitalization increases the risk of septicemia and mortality. If we wait a week, the risk of increasing infection is minimal, presumably because transferrin concentration goes up very quickly, as soon as you provide enough energy and protein.