The Role of Individual Nutrient Deficiencies in Growth Retardation of Children as Exemplified by Zinc and Protein

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When a wheat plant is grown in soil low in selenium, the result is a normally sized plant that has a low selenium concentration in its tissues. When a wheat plant is grown on a soil low in zinc, the result is a stunted plant that has a normal concentration of zinc in its tissues. If similar experiments are repeated with bacteria or laboratory animals, the same result is obtained. In each case, the deficit of the nutrient may be the same relative to a normal subject, but in one case this arises from a low tissue concentration within a normally grown subject, whereas in the other it arises from a small subject with a normal tissue concentration.

Thus, animals kept on a low selenium ration grow normally until they develop severe clinical disease; in the case of rats this is usually hepatic necrosis, and in other species it is cardiac or skeletal myopathy. After they get sick they may well demonstrate secondary growth failure because of the clinical disease, but this is not a primary phenomenon. Mild forms of selenium deficiency in animals are simply characterized by low tissue selenium concentrations and a resultant vulnerability to noxious stresses without a diminution in growth rate.

In marked contrast, rats placed on a low-zinc diet stop growing almost immediately: they can actually die from zinc deficiency without any reduction in the zinc concentration of their major tissues (1,2).

TYPES OF DEFICIENCY

There is clearly a fundamental and quite distinct difference between these two responses to a nutritional deficiency. I suggest that these two types of response should be clearly differentiated from one another, and nutrients classified according to whether they give rise to one response or to the other. The "type I" response is characterized by a reduction in tissue concentration; it first presents with a specific clinical deficiency and is without a primary effect on growth. The "type II" response presents with a primary cessation in growth without a reduction in
tissue concentration and is not normally associated with specific signs and symptoms. It is probable that most nutrients can be classified according to whether the response to a deficiency is primarily of one type or the other, although they may not be so easily classified as selenium or zinc.

Nutrients with Body Stores

For those nutrients that have a body store that serves no immediate function, the picture is clearly more complicated. The prediction is that the first response, in every case, would be a consumption of the body store. Of necessity, in whole-body terms, the concentration of that nutrient would then fall; however, it would only fall in the storage tissues, not in the functional tissues. After the stores are consumed and a functional defect is impending, there may theoretically be either a type I or a type II response.

With a type I deficiency, one would expect to find both an absence of stores and a reduction in tissue concentration; it should first present as a clinical deficiency syndrome. I suggest that iron and iodine fall into this category.

In contrast, with a type II deficiency, although one would expect to find absent or greatly diminished tissue stores, there should be a normal concentration of the nutrient in the functional tissues and growth failure. There is no specific nutrient that seems to behave in this way. Indeed, absence of a body store in the healthy animal seems to be a characteristic of type II nutrients. However, this type of response is precisely what seems to happen with a fuel (energy) deficiency. Thus, the first response to a fuel deficiency is a consumption of the fat stores with no change in the energy content of lean tissue (total body energy concentration is reduced purely on the basis of loss of adipose tissue); at this stage there is no necessary change in the rate of longitudinal growth or lean tissue accretion. After the stores are consumed, the response is clearly a cessation of growth.

I have tentatively classified several nutrients in Table 1.

GENERAL CHARACTERISTICS OF THE DIFFERENT TYPES OF DEFICIENCY

From this starting point, we can predict certain characteristics of the different types of deficiency. With severe deficiency of a type I nutrient, there will be a negative balance for that specific nutrient until clinical signs become manifest, whereas, for a type II deficiency, whole tissue will be catabolized so that the individual will be in negative balance for all the components of lean tissue. Thus, energy, protein, zinc, or potassium deficiency will each lead to a negative balance of the other nutrients in proportion to their relative concentrations in the tissues that are being catabolized; it is only the deficient nutrient that will have a proportionately low excretion.
TABLE 1. Tentative classification of nutrients into type I and type II

<table>
<thead>
<tr>
<th>Type I: initial normal growth, reduced tissue concentration, specific signs</th>
<th>Type II: primary growth failure, normal tissue concentration, no specific signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA. No identified stores</td>
<td>IIA. No identified stores</td>
</tr>
<tr>
<td>Selenium</td>
<td>Nitrogen</td>
</tr>
<tr>
<td>IB. Stored</td>
<td>Essential amino acids</td>
</tr>
<tr>
<td>Iodine</td>
<td>Zinc</td>
</tr>
<tr>
<td>Iron</td>
<td>Potassium</td>
</tr>
<tr>
<td>Copper</td>
<td>Sodium</td>
</tr>
<tr>
<td>Calcium</td>
<td>Phosphorus</td>
</tr>
<tr>
<td>Thiamine</td>
<td>IIB. Stored</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Energy</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td></td>
</tr>
<tr>
<td>Retinol</td>
<td></td>
</tr>
<tr>
<td>Tocopherol</td>
<td></td>
</tr>
<tr>
<td>Cobalamin</td>
<td></td>
</tr>
<tr>
<td>IC. Specific defect in longitudinal growth, specific signs</td>
<td>IIC. None</td>
</tr>
<tr>
<td>Manganese</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
</tr>
</tbody>
</table>

Type I Deficiency

When one conceives of a specific nutritional deficiency, one automatically considers a type I deficiency. It results in a conceptually pleasing and easily envisaged chain of events. The diet is specifically low; this results in a reduced tissue concentration and an identifiable major defect in a metabolic pathway; this in turn gives rise to characteristic clinical signs and symptoms. The diagnosis is relatively straightforward: all that one has to do is measure the concentration of the nutrient in a tissue, measure the vulnerable pool of the nutrient, test the metabolic pathway where the defect lies, demonstrate an in vitro effect of adding the nutrient to some functional system, or recognize the specific clinical signs, whichever is most specific and/or convenient.

Type II Deficiency

The position with respect to type II nutrients (nitrogen, essential amino acids, zinc, potassium, sodium, phosphorus, energy) is quite different in many respects:
indeed, none of the maneuvers that can be used to diagnose a type I deficiency can be used unequivocally to diagnose deficiency of a type II nutrient. Thus, major difficulties, both conceptual and practical, arise when we try to understand, define, diagnose, and study these deficiencies. As growth failure, and hence stunting, is the major long-term characteristic of each of these deficiencies, I consider these difficulties and their implications in more detail.

First, the response to a deficiency—growth failure—is common to a deficiency of each nutrient; therefore, we cannot identify which nutrient is responsible when we observe growth failure.

Many thousands of experiments have been done in animals with diets deficient in one or another of these nutrients; in every case the primary response is a diminution or cessation of growth. As the deficiency progresses, the animal falls further and further behind the controls so that, with time, the animal becomes stunted. If the deficiency is more severe, there is loss of whole tissue, and the animal becomes wasted.

This response has been observed consistently and universally in all species studied, in both acute and chronic experiments, with each of the type II nutrients. So fundamental is this response that it is used to measure a growing animal’s requirement for the nutrient with considerable precision and reproducibility. No other feature has been shown to correspond reliably with deficiency; indeed, there does not need to be any measurable “defect” in any of the animal’s metabolic pathways that can be held responsible for the growth delay. Growth failure, and probably growth failure alone, is thus the \textit{sine qua non} of protein, zinc, energy, etc. deficiency.

In the human context, one would predict that the response to a longstanding mild deficiency of any of these nutrients would be a diminutive person: progressive stunting (with the body in proportion). The extent of the stunting will be in relation to the integral of the degree of shortfall of the nutrient and time. Clearly, with a chronic mild deficiency there will be a corresponding progressive reduction in attained height relative to some acceptable standard through slowing of the growth rate. With an acute severe deficiency there will be loss of tissue leading to wasting, without necessarily time for stunting to occur. The balance between the severity of the deficiency and its duration will determine the relative amounts of stunting and wasting that are produced. Mild chronic deficiencies are expected to be more common than severe acute deficiencies, so stunting would be predicted to be more common than wasting; this is what is observed.

Second, there is a common repertoire of metabolic changes and reductive adaptations that take place in response to a deficiency. However, because whole tissue is being broken down, or at least there is no net synthesis, those nutrients that are in excess relative to the deficient nutrient have to be metabolized and excreted (or, in the case of fuel, put into storage). The balance among the various type II nutrients in the diet is thus very important. In the face of a deficiency of any one of them, we would predict a negative balance for them all.

Third, when a diet that is deficient in any one of these nutrients is given, the
The body has mechanisms to conserve that nutrient avidly. It is for this reason that it is extremely difficult to produce a deficiency of one of these nutrients in the non-growing animal by dietary means; there usually has to be a pathological loss of the nutrient from the body. Thus, urinary sodium and potassium can be reduced to remarkably low concentrations; even zinc losses can be reduced to almost zero (3). This leads, necessarily, to the next implication.

The appropriate rate of growth is the major determinant of the dietary requirement for the nutrient.

For example, children given a diet that supplied just enough energy for them to maintain their body weight without growing were able to remain in zinc balance and maintain their plasma zinc concentration with an intake of only 1.3 μmole/kg per day. When the same children were subsequently given sufficient energy to gain weight rapidly, their plasma zinc fell to very low concentrations; this fall in plasma zinc occurred despite a 10-fold increase in the amount of zinc consumed (14 μmole/kg per day) (4). Even with this relatively enormous zinc intake, zinc was limiting lean tissue synthesis (5-7): it is noteworthy that these children did not develop the signs classically ascribed to zinc deficiency; they simply did not synthesize tissue requiring more zinc than was supplied.

The implication of these observations is that no other sign, except for growth failure, is to be expected from a deficiency of one of these nutrients unless the deficiency is very profound.

There is a corollary of this observation that at first sight seems contradictory: it is that one would expect a diet that has a sufficiently low concentration of one of these nutrients to give clinical signs, other than growth failure, to produce signs in adults before children. This hypothesis is a direct consequence of the higher maintenance energy requirement of the child. The protein requirement of the child, for maintenance, is about the same as it is for the adult, 0.6 g/kg per day (8); however, the energy requirement for maintenance of the child is about 400 kJ/kg per day, whereas, that for the adult is about 160 kJ/kg per day. Hence, an adult taking his resting energy requirement must have 6% of the energy as protein, whereas, a child only requires about 2.4% of the energy as protein. Therefore, in a community, we should not expect to find anything other than growth failure in children: if the local diet is sufficiently deficient to give rise to other clinical signs, these should be manifested in adults before children. However, there is an extremely wide gap between the level that will give rise to growth failure and the level that will cause any other obvious feature of deficiency, so that even where growth failure is common, clinical signs should be very rare.

Because growth rate is the major determinant of the requirement for these nutrients, when we supply the missing nutrient there should be a catch-up growth response. We should be able to use this response as a test to diagnose that the growth failure was secondary to lack of a particular nutrient. However, even this, unfortunately, is not necessarily so. When the deficiency was developing, whole tissue was being catabolized. Consequently, there will be a deficit of all the components of that tissue irrespective of which nutrient was originally deficient. There
will consequently be a greatly increased dietary requirement for all the nutrients during catch-up growth. This means that a catch-up response to giving the originally deficient nutrient may be short-lived, and the rate of catch-up may now be limited by another nutrient that, in the basic diet, was present in perfectly adequate amounts to sustain normal growth. The important variable will be the ratio of the requirement for normal growth and that for catch-up at an observable rate for each of the nutrients in the diet. A secondary catch-up response cannot then be taken as evidence of an original deficiency. The dietary requirements for catch-up growth are unknown. They are obviously of enormous importance.

Supplementation with the right nutrient should, of course, cause growth at at least the normal rate, unless more than one nutrient is deficient for normal growth rates: normal growth is sufficiently slow in man to make diagnosis by supplementation a correspondingly slow and difficult process.

Fourth, one response that seems to be common to a deficiency of each of these nutrients is anorexia; this is corrected if the nutrient is supplied. Thus, if a child with zinc deficiency is supplemented with zinc, he will regain his appetite and have an increased intake of protein, energy, potassium, and even nonsupplemental zinc in response to the specific supplement (9). Clearly, with these nutrients and this type of response, it is extremely difficult to interpret dietary intake data. The increase or decrease in the intake and utilization of the nutrient under consideration may be caused by a deficiency of a different nutrient altogether. There will clearly be complex interactions among these nutrients.

The etiology of the anorexia is unknown. It may be the deficiency itself; however, it may also be the relative surfeit of the other nutrients, which have to be metabolized and excreted to prevent them from being toxic (6,10). Since anorexia is not a consistent response, the latter may be more likely.

Because growth will be limited by the most deficient nutrient, it is only possible to have a "deficiency" in the classical sense with one type II nutrient at a time—the limiting one. Thus, even if a diet contains very reduced quantities of a particular nutrient—protein, for example—no response to supplementation and no specific consequences of that particular deficiency are to be expected if another type II nutrient is even more deficient.

Fifth, when a dietary supplement is given that does not contain all the nutrients required for new tissue synthesis, the rate of growth will be determined by the most limiting nutrient in the new diet (basic diet plus supplement), not in the original diet or in the supplement alone. Indeed, by diluting the original diet, an incomplete supplement can make a deficiency worse; there are probable examples of this in the literature (11).

Clearly, if an unbalanced supplement is given, the other nutrients in the supplement will be used inefficiently. The degree of inefficiency will be related directly to the magnitude of the discrepancy or imbalance between the actual limiting nutrient in the diet as a whole and the nutrient under consideration. If the supplement is almost devoid of any particular type II nutrient, then the supplement will be used with a zero efficiency unless that nutrient is in excess in the basal diet, in which case the efficiency of utilization will be related to the relative excess in the
basal diet over the needs for accelerated growth. If we observe an inefficient use of nutrients (or, more commonly evaluated, energy), then we can infer that the diet is imbalanced and one of the type II ingredients is limiting growth and efficiency. Gross inefficiency is almost universal in reported supplementation trials: none of them have been formulated to contain all the type II nutrients in what is thought to be adequate amounts.

As yet a further complication, the response to the supplement and the required balance of nutrients in the supplement, will depend on the precise mix of tissues that should be laid down. This will depend, in turn, on the age of the subject, the degree of wasting and stunting that has to be made good, and the composition of the required new tissues. Clearly, the dietary requirement for skeletal growth, for muscle synthesis, for adipose tissue, and for skin synthesis will potentially differ, but by how much, in what way, and whether this is ever a major factor has not been explored.

Sixth, if conventional techniques are used to diagnose a deficiency of one of these type II nutrients, the results are likely to be totally misleading. Clearly, there is little point in doing a muscle biopsy and measuring the gross threonine or zinc concentration, for example, in that biopsy. Experience has shown that this approach simply does not work. If there is a change in the nutrient of concern in the biopsy, the change is just as likely to result from a deficiency of one of the other type II nutrients, from an alteration in metabolism consequent on a deficiency of a type I nutrient, or even from a metabolic alteration unrelated to nutrition as it is likely to be secondary to a deficiency of the specific nutrient under the spotlight. It should be noted that a small percentage of changes in type II nutrient tissue concentration can occur as the metabolic state alters; for example, structural protein to soluble protein ratios will affect the essential amino acid concentration, as will the intensity of protein synthesis. This would explain the small fall in tissue zinc concentration with an essential amino acid deficiency when there is none with zinc deficiency itself (12). In this way, a zinc deficiency, energy deficiency, or an infection is as likely a cause for a low albumin, prealbumin, or retinol-binding protein concentration in plasma as is a protein deficiency (13). Herein lies the difficulty: the response is not specific to any particular nutrient.

I tentatively suggest that much of the controversy that surrounds the definition of a deficiency, the signs and symptoms of deficiency, the diagnosis of deficiency, and the requirements of those nutrients that I have classified as type II nutrients stems from attempts to conceive of them as fulfilling the classical nutritional maxims that underlie, and have been so useful in evaluating, deficiencies of iron, iodine, the water-soluble vitamins, and other type I nutrients. The type II nutrients have to be considered together as fundamental cellular constituents.

NUTRIENTS THAT AFFECT GROWTH DIRECTLY

As with all schemes, there is a complication with this simple classification of nutrients into those that reduce their tissue concentration with continued growth
and those for which the response is cessation of growth and avid conservation of
the nutrient's tissue concentration. In the context of longitudinal growth, what
happens if the specific metabolic defect of a type I nutritional deficiency itself in-
terferes with longitudinal growth? Several nutrients, such as manganese, vitamin
D, vitamin C, and copper, potentially fall into this category.

A manganese deficiency in animals leads to a specific defect in proteoglycan
synthesis (probably on the basis of reduced activity of UDP-galactosidyl transfer-
ase I, a manganese metalloenzyme), leading to cartilage dysplasia and abnormal
growth. However, not only is there a recognizable pathological lesion but also ani-
mals on a manganese deficient diet continue to gain weight, so that although they
are stunted, they are not any lighter than the controls (14). This is in contrast to
the stunting of zinc or protein deficiency, where the short animal is either in pro-
portion or is, more usually, wasted.

Similarly, vitamin D deficiency gives rise to stunting—the classical cause of nu-
tritional stunting—but is also associated with specific symptoms and signs and
characteristic bone changes: the vitamin-D-deficient child is not simply diminu-
tive. Vitamin D deficiency is associated with a clinical myopathy and muscle pain
but not with wasting per se.

Interestingly, although copper deficiency is associated with gross osteopenia
(secondary to a defect in lysyl oxidase, the enzyme necessary for cross linking
the collagen molecules of bone matrix), it does not seem to be associated with
stunting.

Again, vitamin C deficiency, which also leads to defective collagen synthesis,
gives distinct pathological bone changes and specific signs in other systems that
are relatively easily diagnosed; it does not seem to give rise to simple short stature.

The essential difference between these nutrient deficiencies and a type II nutri-
ent deficiency is that these deficiencies all give rise to clearly pathological features
in bone or cartilage that must be there before there is stunting. These nutrient de-
ficiencies, therefore, may present a theoretical difficulty in anthropometric classi-
fication but are unlikely to present any difficulty clinically—they are not associated
with simple diminutiveness.

ARE TYPE II DEFICIENCIES AN IMPORTANT CAUSE OF STUNTING?

Having laid the conceptual framework and considered some of its implications,
we must ask ourselves if it is likely that deficiencies of any of the type II nutrients
are, in practice, limiting growth in any substantial population group.

Because we do not yet know the precise requirements for normal growth of chil-
dren for each of these nutrients, and we do not know the requirements for acceler-
ated growth for any of them, the question of dietary adequacy, or inadequacy,
cannot be decided at this time. It is thus not possible to say, from intake data,
whether any type II nutrient limits growth, with the possible exception of fuel. We
do have estimates of the energy requirements for both normal and accelerated gain
in weight but not for gain in height.
It must be clear that the demonstration that a diet is adequate for only energy, protein, and the type I nutrients that have received attention is very far from addressing its adequacy as a diet. Assessment of the requirements for catch-up growth have not been seriously or systematically investigated.

I am unaware of any supplementation study in which even "informed guesses" of the requirements for catch-up of all nutrients known to be essential have been made and the response to giving such a supplement observed. Virtually all supplementation trials have either looked at the effect of a single nutrient alone or, more commonly, have tried to obtain a response from the cheapest available source of presumed adequate food without there being a clear idea of what nutrients are actually being given, what their availabilities are, how they relate to the requirements, and without an attempt to tailor the supplement to the nutrient composition of the basal diet. It is noteworthy that it is the mineral elements that have, by and large, been ignored despite the fact that most cultures place emphasis on minerals in culinary practice (vide infra). None of the field studies supplemented the diets with even a simple mineral mix. This situation is in marked contrast to the practice of virtually every agriculturalist and advisor in animal nutrition, where experience has led to an appreciation of the importance of the mineral content of the diet. We could learn from detailed attention and continuing research effort directed to preparing and refining the highly complex dietary supplements used for different aspects of commercial animal production.

Potential Catch-Up: What Should Be the Target?

What is the potential for catch-up in a stunted child? How far from this potential are the reported results of feeding trials? We do not know. In an attempt to get some idea of what could be achieved, the records of 417 children consecutively admitted to the Tropical Metabolism Research Unit (TMRU) with severe malnutrition were examined. The children were weighed daily and had height measured weekly to the nearest 0.5 cm. They were treated as previously described (15). The median age of the children was 12 months, and the median period of observation 9 weeks. The results are shown in Table 2. The range of height gain was from 0

<table>
<thead>
<tr>
<th>Height gain (mm/day)</th>
<th>Admission to discharge</th>
<th>Admission to &gt; 90% wt. for ht.</th>
<th>&gt; 90% wt. for ht. to discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.1</td>
<td>5%</td>
<td>36%</td>
<td>14%</td>
</tr>
<tr>
<td>0.1–0.3</td>
<td>26%</td>
<td>20%</td>
<td>14%</td>
</tr>
<tr>
<td>0.4–0.8</td>
<td>59%</td>
<td>35%</td>
<td>46%</td>
</tr>
<tr>
<td>&gt; 0.8</td>
<td>11%</td>
<td>8%</td>
<td>26%</td>
</tr>
<tr>
<td>Less than normal</td>
<td>31%</td>
<td>56%</td>
<td>28%</td>
</tr>
<tr>
<td>Greater than normal</td>
<td>70%</td>
<td>44%</td>
<td>72%</td>
</tr>
</tbody>
</table>

*From M. Golden and S. Walker (unpublished data).
to 9.5 cm during the 2 to 3 months of observation. Clearly, some of the children were capable of enormous height spurts.

The data were analyzed separately for the period of accelerated weight gain (from admission to 90% weight for height) and for the subsequent weeks, when their wasting had been corrected. Over 70% of the children gained height at more than the normal rate for this age; 44% gained significant height while they were gaining weight rapidly; after repletion of weight for height, 26% of the children gained height at more than twice the standard rate. This is despite the fact that the diets that the children receive are known not to be optimal. The children exhibit an abnormal body composition after they have recovered weight for height. (16). Significantly, they have a limitation of lean tissue synthesis, leading to abnormal muscle tissue (17) and, at this stage, very inefficient growth (5). Further, we have observed an acceleration of weight gain at an increased efficiency with zinc supplementation (5, 6). When we gave children additional zinc throughout recovery, they synthesized much more lean tissue than fat tissue (7). It seems that our diets are still limiting in type II nutrients; we are certainly not achieving the full potential height gain.

Nevertheless, it is clear that a rapid, measurable, and substantial gain in height, of the order of 2.5 cm/month, can be achieved over a relatively short observation period in about a quarter of our children with what we know to be an inadequate intake. Clearly, with the proper supplementation, very prolonged studies with extremely precise measurements should not be required; the more inadequate our supplement, the harder it will be to show a difference. Perhaps this is why studies of height gain have a reputation for difficulty.

Against this background, we can examine the results of the various supplementation studies in third world populations. These have been reviewed by Beaton and Ghassemi (18). In these studies the supplement was usually dried skim milk, various combinations of wheat and soya, or local foods. The outstanding conclusion is that the supplements made very little difference, sometimes reaching statistical significance, sometimes not, but never achieving substantial gains. The harder it is to show a statistical difference, the less likely that difference is to be of biological significance. At some stage it is pointless to continue to pursue a statistical result, which can then be hailed as a "success," when the difference is biologically trivial and clearly overshadowed by much more important variables, which are not being considered: the biological significance of all these studies is in doubt.

One way to examine the above mentioned data is to look at the efficiency of weight (or height) gain. The positive studies report an effect of the supplement of up to 1 kg/year. This implies that the supplement was responsible for an increased weight gain of 2.5 g/day. At an energy cost of tissue synthesis of 20 kJ/g (5 kcal/g), the energy needed to lay down this tissue amounts to only 50 kJ/day (12.5 kcal/day); this is a minute amount. The dietary supplements were usually substantial (16.6–33.6 MJ/day; 300–800 kcal/day); clearly the supplement was used very inefficiently. In most studies about one-third of the supplement actually is taken by the target subject because of "leakage," food substitution, etc.; however, there is still a substantial difference between the supplement and the observed effect
ZINC AND PROTEIN DEFICIENCIES

(420–1,120 kJ/day versus 50 kJ/day; 4 to 12% efficiency). The poor efficiency is probably, in part, related to recurrent infection and malabsorption. However, it is precisely the result we would expect if insufficient attention was paid to one of the type II nutrients; we know that this was indeed the case in every study.

PROTEIN

Most of the studies that have reported a height gain with supplementation have used a milk- or soya-based supplement. Unfortunately, it is not possible to be certain whether this is an effect of the protein per se or whether it is caused by one of the "fellow travelers" added to these diets—phosphorus is an obvious contender in this respect. It has been said that these points are of little practical importance. That would be so if it were really only protein involved, but not if a "fellow traveler" proved responsible for the observed effect. Should we, then, be spending time, effort, and money to build fish farms on the basis of results obtained with milk supplements? Only if protein deficiency is in fact responsible.

The most important study is probably that of Malcolm (19,20). He studied a community of children living in an isolated boarding school in the New Guinea highlands. The whole community was fed exclusively on taro or sweet potato; the children were very stunted, even by local village standards. The children were divided into four groups: one received a supplement of 75 g skim milk powder daily; a second received 30 g margarine daily; the third had their intake of taro increased by a factor of 1.67; and the last group received no extra food. The results are shown in Table 3. The skim milk led to an incremental gain in height and weight

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Extra diet (1.67-fold)</th>
<th>Margarine (30 g)</th>
<th>Skim milk (75 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplement for 13 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>35</td>
<td>22</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.6</td>
<td>7.4</td>
<td>9.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>1.10 ± 0.12</td>
<td>1.54 ± 0.13</td>
<td>0.96 ± 0.11</td>
<td>2.32 ± 0.11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.50 ± 0.13</td>
<td>0.47 ± 0.14</td>
<td>1.05 ± 0.18</td>
<td>1.21 ± 0.10</td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
<td>+ 0.17 ± 0.13</td>
<td>+ 0.77 ± 0.17</td>
<td>+ 2.28 ± 0.35</td>
<td>− 0.13 ± 0.14</td>
</tr>
</tbody>
</table>

| Supplement for 32 weeks|                      |                        |                  |                  |
| Control                | 30               | 30                     | 26               |
| Skim milk (10 g)       | 1.75 ± 0.17      | 3.23 ± 0.13            | 3.45 ± 0.14      |
| Skim milk (20 g)       | 1.34 ± 0.18      | 1.98 ± 0.14            | 2.92 ± 0.13      |
| Triceps skinfold       | + 0.78 ± 0.18    | + 0.26 ± 0.18          | − 0.09 ± 0.15    |

*Data from Malcolm (19) and Lampl et al. (20). All results are expressed as mean ± SEM of increments over the study period.
with no change in skinfold thickness. Provision of energy, on the other hand, led to a substantial gain in skinfold thickness and no incremental gain in height.

It is clear that energy was not limiting height gain, for the additional margarine did not have any effect although it produced an increase in fat stores. The extra diet did not increase body weight, but it did increase both fat stores and height. Was there some nutrient in the diet in lower relative concentration than energy that permitted lean tissue to be converted to height gain? If so, it is clear, as could have been predicted, that the nutrient requirements for lean tissue and skeletal tissue growth are different. The additional milk produced the largest increment in height, with an actual reduction in fat stores. In effect, the additional milk contained some ingredient(s) that permitted conversion of soft tissue into skeletal tissue. This is despite the fact that the diet did not contain the additional energy required for accelerated height gain, and so endogenous sources had to be used, and skinfold declined. It is probably correct to say that energy deficiency does not lead to stunting in the presence of fat stores. Fat stores can be demonstrated in most stunted children. The result of this first study was confirmed, with a graded response to the two levels of supplementation, in the second study.

What were the components of the dried skim milk that produced this response? Certainly, total protein or one of its “fellow travelers” (particularly essential amino acids, zinc, phosphorus, or calcium) is a likely contender.

The question of what component of cow’s milk is responsible cannot be answered. However, in a study of Finnish infants, Salmenpera et al. (21) compared the growth of exclusively breast-fed infants with those given formula. The breast-fed infants progressively fell behind the formula-fed infants, so that by 9 months of age 45% of them, versus 18% of the formula-fed infants, were more than 1 SD below the standard length. There was no difference in the children’s weight. Skinfold measurements showed the breast-fed infants to have substantially more storage of fat. Obviously, energy or total breast milk intake was clearly not limiting height gain. Here again, as with the New Guinea children, the infants consuming cow’s-milk-based formula were longer and thinner than the control group. However, in this study, cow’s milk was compared to human milk, so that many of the confounding variables were different. Within the breast milk group itself, no correlation could be found between breast milk protein concentration, protein intake, or protein intake per unit body weight and either growth velocity or changes in relative length. As expected, the fat concentration of breast milk and the calculated fat intake were not related to gain in length. However, there were substantial differences in the protein intake of the two groups of infants. The increased protein supply was thus common to the two studies and must be the prime candidate nutrient for the effect. There will have been marked differences in other nutrients as well. For instance, the difference in phosphorus concentration of human and bovine milk is relatively greater than the difference in protein. Phosphorus intake was also much higher in Malcolm’s supplemented children. Was protein, phosphorus, or some other nutrient altogether responsible?

However, it is equally clear that many of the supplementation studies that have
used skim milk have not produced any increment in height, and in all the studies, including those of Malcolm, the actual increment in height was much less than the potential increment we think should be achieved if a "full supplement" had been given.

At present the question of whether substantial sections of the population have stunting secondary to protein deficiency must remain open. By analogy with animal studies and the responses to skim milk powder, it is likely that at least in some areas protein deficiency will transpire to be the limiting factor for longitudinal growth.

**ZINC**

The most carefully conducted studies of zinc supplementation have been done in the United States by Hambidge's group. They have shown unequivocally that additional zinc leads to increased rates of gain in length in stunted male infants and children in Denver.

In the first study (22), infants were randomly divided into two groups. One was given a proprietary infant formula (1.8 mg zinc per liter), the other the same formula with supplemental zinc (5.8 mg zinc per liter). The results of this study are shown in Table 4. After 6 months the male infants receiving the supplemented formula were over 2 cm longer and 500 g heavier than the unsupplemented infants. There was no difference in the female infants. It should be emphasized that these infants were all "normal" infants—they were not selected on the basis of having been short at birth.

Hambidge's next study (23) involved preschool children 38 to 60 months of age (mean age 50 months) who were selected on the basis of being below the 10th centile of the Iowa standards. The test subjects were calculated to receive an addi-

### TABLE 4. Growth increments and plasma zinc levels at 6 months of age in infants fed a proprietary formula with (5.8 mg Zn per liter) or without (1.8 mg Zn per liter) zinc

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Supplemented</th>
<th><em>p</em> value</th>
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</thead>
<tbody>
<tr>
<td><strong>Males (n)</strong></td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>17.36 ± 0.88</td>
<td>19.46 ± 0.48</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.99 ± 0.27</td>
<td>4.53 ± 0.11</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>8.36 ± 0.42</td>
<td>8.85 ± 0.23</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma zinc (µg/dl)</td>
<td>69.5 ± 3.2</td>
<td>80.5 ± 3.7</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td><strong>Females (n)</strong></td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>16.73 ± 0.48</td>
<td>16.36 ± 0.52</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.77 ± 0.20</td>
<td>3.94 ± 0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>8.33 ± 0.33</td>
<td>8.48 ± 0.24</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma zinc (µg/dl)</td>
<td>73.9 ± 2.2</td>
<td>72.5 ± 4.1</td>
<td>NS</td>
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</tbody>
</table>

*Data from Walravens and Hambidge (22), expressed as mean ± SEM.*
tional 4.2 mg zinc/day (0.3 mg/kg per day) based on estimated compliance; the control subjects were given placebo. The results are shown in Table 5. There was a highly significant increase in height velocity of the male children with an improvement in Z scores of height for age. Again, there were no significant changes in the female children.

There have been reports of growth responses in adolescents with delayed puberty in the Middle East given zinc supplements (see 12). However, in the only well-controlled study (24), there was no improvement with zinc supplementation. The other studies, although suggesting that zinc deficiency was responsible for stunting, were not well controlled and inconsistent, and much of the data were not presented.

Signs of severe zinc deficiency do occur in malnourished infants (25), and there is a suggestion that those with the worst zinc status are the most stunted (4).

Several conclusions are possible from these studies. First, zinc deficiency in man gives rise to limitation of longitudinal growth, as it does in experimental animals. Second, males are much more susceptible to zinc deficiency than females. If severe zinc deficiency is evident in children with malnutrition requiring admission to hospital, then, because of the large difference between the dietary intake necessary to cause growth retardation and that necessary to give clinical disease, it is likely that growth limitation caused by zinc deficiency is quite common.

On the other hand, there is a marked sex difference in the response to zinc supplements. If zinc was limiting growth, then one would expect boys to be much more stunted than girls; this is not the case.

As in the results of supplementation with protein-enriched sources, the increments in height with zinc supplementation were very modest. In certain circumstances zinc may well be the limiting nutrient, but clearly, if this is the case, when zinc is given, some other dietary constituent quickly becomes the limiting nutrient. Dried skim milk is not a particularly good source of zinc. One could speculate that in those studies in which there was a modest response to milk powder, zinc quickly became the second limiting nutrient for growth, whereas when zinc was given, protein or phosphorus became the limiting nutrient. This would explain

<table>
<thead>
<tr>
<th>TABLE 5. Growth velocity and changes in Z scores for preschool stunted children given a zinc supplement (4.2 mg/day)*</th>
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<tbody>
<tr>
<td>Males (n)</td>
</tr>
<tr>
<td>Height velocity (cm/year)</td>
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<tr>
<td>Weight velocity (kg/year)</td>
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<tr>
<td>Change in height Z score</td>
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<tr>
<td>Females (n)</td>
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<tr>
<td>Height velocity (cm/year)</td>
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<td>Weight velocity (kg/year)</td>
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<td>Change in height Z score</td>
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why in each case the response was definite but modest. Of course, these arguments would apply with equal force to any of the other type II nutrients.

MINERAL NUTRITION

I am unaware of any trials of potassium or sodium supplementation or of attempts to measure the influence of potassium or sodium on growth. This may be because there are extremely effective physiological mechanisms to conserve these elements, so that an individual can remain in balance on a very low intake. But what of the requirements for growth? These are assumed to be met, but are they? It is worth remembering that large amounts of sodium can be lost in tropical climates from perspiration and that sodium and potassium losses are characteristic of diarrhea, a common complicating factor in these children. Much attention has been paid to the acute effects of electrolyte depletion. Could the chronic effects be growth failure? This question has not been seriously addressed. It may be significant that positive nutritional effects have been reported from giving oral rehydration fluid out of all proportion to the perceived nutritional contents of these solutions.

Mineral elements have received very little attention from those interested in child growth in the tropics; however, there are considerations, apart from the example of animal nutrition, that may indicate their importance.

Mineral Availability from Traditional Diets

There are strategies used by most traditional cultures to increase the mineral availability from their diets. Plant seeds and starchy roots contain metal-complexing compounds, principally phytic acid (inositol hexaphosphate). This is the phosphorus "store" of plant tissue. The phosphorus from phytate and the mineral elements it complexes are unavailable to man. Traditional culinary practices have evolved three general methods of improving the availability of minerals from vegetable diets.

First, many staples are fermented by the peoples who first used the staple. The Amerindians soak cassava in water troughs for days before it is eaten; the Polynesians bury breadfruit until it has almost liquefied before it is eaten; wheat flour is mixed with yeast and fermented; soy beans are ground and then fermented to make bean curd.

Second, the seed is allowed to germinate so that the endogenous phytase breaks down the phytic acid. An example of this would be the sprouting of beans widely used in Southeast Asia. Both of these techniques involve breaking down phytic acid, one with fungal phytase and the other with endogenous phytase.

The alternative third strategy is to increase the mineral content directly. The North American Indians burn certain plants (about 40 different species are used) and add the ash to maize meal (26). This tradition of adding plant ash to maize is common throughout all the tribes of North America (27). The practice of burning
plants and adding the ash to food is also widespread among African tribes still living in their traditional way (28,29), South American Indians (30,31), and New Guinea natives (32). The ashes used are all rich in potassium, calcium, magnesium, phosphorus, iron, zinc, and the other trace elements; they may contain the "overlooked factor" that has been lost or made unavailable by modern methods.

Populations that are displaced have either changed from their traditional culture or have started to consume unfamiliar foods or both. They cease to prepare their staple foods in the traditional manner and give up the practice of adding plant ash to their foods. Thus, federal "aid" in the form of pure "unadulterated" maize meal that is supplied to the reservations may be far inferior to the traditionally prepared maize (33).

The net result of these changes will be mineral malnutrition. Many of these elements are type II nutrients, as I have defined them, and clearly magnesium, calcium, and phosphorus are central to skeletal growth.

CONCLUSION

We must conclude that the place of mineral elements, electrolytes, macroelements, and the trace elements, has been neglected for too long in the investigation of stunting. The place of protein deficiency as a cause of stunting has hardly been looked at because most investigators thought that protein deficiency gave rise to kwashiorkor, and it is well known that kwashiorkor children are not particularly stunted. Too much attention has been paid to diets and not enough to nutrients in studies of human growth (in contrast to the animal studies, where the exact opposite obtains). There has been almost no basic metabolic research into the nutritional determinants of longitudinal growth to give a sound nutritional basis to the field studies. Most of the field studies have been conducted because of inappropriate pressure to "do something quickly" about an enormous and highly complex problem. They have thus, for the most part, been naive and expedient and not posited on sound metabolic principles.

There is a requirement, in the investigation and treatment of stunting in the third world, for a series of physiological studies to be conducted so that we can increase our understanding before further large-scale, expensive, and difficult field studies are undertaken.

ACKNOWLEDGMENTS

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REFERENCES


DISCUSSION

Dr. Tomkins: Energy and protein intakes in zinc-supplemented children were about twice as high as in nonsupplemented children. The energy cost of tissue deposition in zinc-supplemented children was about 7 kcal/g versus about 11 kcal/g in the nonsupplemented children. Could we partition the amount of growth that is attributable to the increase of food intake as a result of the effect of zinc on appetite as opposed to the amount of growth that results from improved metabolic efficiency?

Dr. Golden: This is an extremely difficult question. We really don't have the data to answer it. In many of the children we do not see an appetite response to zinc, but we do see an increased metabolic efficiency. The balance of nutrients in the diet seems to be absolutely crucial. The most limiting nutrients in a diet will be used very efficiently; the rest of the nutrients will be used in proportion to the limiting nutrients. Any excess has then to be excreted, so there is a measure of inefficiency of use of all nutrients except for the limiting one. The degree of inefficiency of use for each nutrient seems to be related to this imbalance. In all the experiments carried out in rats, high-protein diets have been used. The protein, in the face of a zinc deficiency, is used very inefficiently and is broken down and excreted; the anorexia that is seen in rats seems to be related to this. If you take a rat and put it on a zinc-deficient diet, the rat becomes anorectic; if you then get the balance right by reducing the protein content of the diet, anorexia stops, and the rat uses its food very inefficiently and becomes slightly obese. The answer to whether you will get anorexia or inefficient use depends on the balance of nutrients in the diet. All these nutrients that I have called type II nutrients are very closely related to each other, and deficiency of one leads to loss or imbalance of them all. I think we have got to think in terms of the proportion of all these nutrients in the diet in relation to one another.

Dr. Mukherjee: What was the duration of the hospital stay of the 417 children whose rate of gain in length you presented? Since these children did not receive a zinc supplement, to what do you think their rapid linear growth can be attributed?

Dr. Golden: These children were unselected consecutive admissions to the ward. The median hospital stay was 9 weeks. We know that the diets that were given to these 417 children did not contain sufficient zinc. There were probably many other nutrients in the diet that were there in insufficient amounts. The children were growing at the rate, I presume, of the most limiting nutrient in our diet. The reason I presented these data was to show what can be achieved with a regular rehabilitation diet in a metabolic ward when treating malnourished babies: catch-up in height does occur; it occurs quite rapidly and is easily measurable. We are not talking about millimeters over weeks, we are talking about centimeters. I would suggest that if one does not see this type of response, one should analyze the diet given to the children and look for some other type of deficiency that remains uncorrected.

Dr. Waterlow: I like very much your distinction between type I and type II deficiencies.
This is a clarifying concept. The type II deficiencies seem to refer to structural components of the cell; one could think of potassium or magnesium as essential components of the cell. I wonder where you would put essential fatty acids. You surely remember the original work long ago by Kosterlitz and colleagues (5), who showed how the ratio of phospholipids to protein and RNA remains constant but is altered in relation to DNA. Secondly, you mentioned biopsies as being useless. I would like to suggest that they are not useless for these components if you relate them to DNA.

Dr. Golden: Essential fatty acids might be an example of nutrients that are stored, and when the store is depleted, they behave as type II nutrients. The reason I say biopsies are useless is that when you find that cell zinc or protein per DNA is low, you are immediately tempted to say that this is zinc or protein deficiency. What we are actually looking at is a metabolic change, which could be caused by a deficiency of any of these nutrients or of energy or by a metabolic aberration unrelated to nutrition, for example, infection.

Dr. Waterlow: I agree with that; I call it depletion, not deficiency. However, I was really trying to get back to what Dr. Milner said about hyperplasia and hypertrophy. You get a hypotrophy—small cells.

Dr. Golden: It is worth looking for, but not to diagnose a deficiency of that particular nutrient.

Dr. Kittima: In which type of nutrients do you classify calcium?

Dr. Golden: As you can see, my classification is incomplete. I haven't classified many of the nutrients. I have classified the ones I personally have thought about and looked at the literature on and don't have that much difficulty in deciding how to classify them. However, I have great difficulty in deciding where calcium and magnesium should go. Phosphorus we have heard should clearly be classified as a type II nutrient; calcium, I'm not sure about.

Dr. Martorell: You mentioned that supplementation trials have not shown much of an effect on growth. I think the basis for this view is the review article by Beaton and Ghasssemi published in the American Journal of Clinical Nutrition (1), which everybody quotes. I think this article really underestimates the potential impact of nutrition because, first of all, it doesn't include all the trials that have been carried out. For example, it doesn't include the INCAP trial, which did show quite a pronounced effect on linear growth. On the other hand, it includes many so-called experiments that weren't experiments at all but evaluations of efforts to provide food to poor people, CARE programs and so on, with very poor research designs. As you mentioned, often the food was given to families and not directly to children; nobody knows whether the child actually ate any of the food. Sample size of some of these studies was very small, and many studies had no control group. It is dangerous to conclude from such studies that supplementation and dietary improvements will not have an impact on growth.

Another comment concerns Malcolm's study (2) in New Guinea, from which one would conclude that protein has a role. But the diet in that area is a very unusual diet based on root crops, which are very poor in protein. This conclusion may not apply to many regions in the world where the staple diet is made up of cereals, legumes, and so on. It may be a very different situation.

Dr. Golden: I agree with you entirely about the unusual diet in New Guinea and the fact that Malcolm's study is the only one really to show this type of effect so clearly. It may well be that protein is limiting in New Guinea and something else in most other places. The nature of the biological response in man to protein deficiency is one question; whether it actually occurs in practice is a totally different question, and I don't think we have addressed that question.
Your comments about Beaton's review are well taken; the Atole Fresco study (3) as well as a number of other studies have shown a statistically significant effect. However, I wonder how biologically significant it is to get a 1- or 2-cm difference in a population that is 12 cm short. When we look at what happens to patients with celiac disease or to what happens in the ward when we give what we now know to be a poor diet because we just don't know what the requirements for catch-up are for any of the nutrients, we should see a much better and biologically significant response than has been reported.

Dr. Tomkins: There are obviously different components in the impact of systemic infection on nutrition, whether it is weight or height gain. One of them is anorexia. Another is the increased energy cost of weight gain, which has been documented to a limited degree. In acute infection, plasma zinc goes down, but whole-body zinc status is not going to change. Could you give us your opinion on whether there is a role for zinc in the increased energy cost of growth in systemic infection, or is this just a transient decrease in plasma levels that has no physiological impact on weight gain?

Dr. Golden: The short answer is "yes." However, our ignorance is so vast on the requirements for normal growth of many of these nutrients in humans, let alone different requirements necessitated by accelerated growth, that we cannot judge the diets. I don't think we have sufficient information or even the correct concepts to study this properly. The reduction in plasma zinc in response to an infection is a redistribution within the body. The response to an infection is a change in metabolism. I think we will get similar changes in metabolism in response to deficiencies of type II nutrients. I think there are common final pathways, and when we trace them back, quite arbitrarily we ascribe a metabolic aberration to what we consider may be the cause—deficiency, infection, etc.—without considering other possibilities.

Dr. Ousa: Did you find episodes of infection during recovery from malnutrition?

Dr. Golden: Children who had recovered on our diets, which we now know to contain insufficient zinc, had small thymuses and had a defect in cell-mediated immunity. We did not record an increase in infection in these children, however. The number of children we looked at was small, and they were housed under relatively hygienic conditions.

Dr. Valyasevi: Would you care to comment on the relationship between zinc and vitamin A, because in many areas there are good indicators of deficiency in both.

Dr. Golden: Clearly, there is a relationship between zinc and vitamin A. The progression and exacerbation of vitamin A deficiency despite quite large amounts of supplemental vitamin A may well be related to the sort of concepts I have considered. We put a child into an anabolic phase so that he had to make tissues and gain weight when we force fed him or put a tube down and gave him a lot of energy. In these circumstances we find exactly the sort of thing I have shown—acute depletion in zinc. Under these conditions we would expect there to be problems with epithelia, and we will undoubtedly find a synergism between preexisting vitamin A deficiency and an acutely induced zinc deficiency despite the fact that we have given a lot of zinc to the children. Yes, I think this is a very important point. On the contrary, I am not convinced about the value of retinaldehyde dehydrogenase measurements, because there seem to be very small changes in the dehydrogenase activity even in the face of severe zinc deficiency.

Dr. Colombo: A study is going on in Chile in which undernourished children are given a formula with zinc. The preliminary results show that they are growing better than the control group. However, the copper status of these children has also been evaluated, and it appears to be very low, which was related to the growth deficit. Do you have any comment on this?
**Dr. Golden:** Copper deficiency could give rise to stunting because of reduced lysyl oxidase activity and reduced desmosine formation. Whether it in fact does, I am not sure. Milk is exceptionally low in copper, particularly cow’s milk, which is much lower than human milk. If we look at the difference in rates of growth of premature infants (who are born with low hepatic copper stores because they haven’t laid down hepatic copper during the last trimester) on breast milk and on cow’s milk, we see that their longitudinal growth is better on cow’s milk than it is on breast milk. Shaw’s balance studies (4) in these infants showed that they had good length growth despite very deficient copper intakes and despite the fact that they were in negative copper balance. Copper may fall into the same class as calcium. Longitudinal growth continues even though there is marked calcium deficiency, but the child ends up with thin bones. We certainly do not get any relationship in our children between longitudinal growth and changes in superoxide dismutase, which we are now using as a measure of copper status.

**Dr. Rappaport:** Zinc deficiency modifies immune tolerance and the immune system. How does this relate to the condition we are dealing with? Can it specifically be the cause of an increased incidence of infectious disease, or is the situation too complex to relate anything specifically to zinc deficiency?

**Dr. Golden:** Severe zinc deficiency creates problems with cell synthesis and cell turnover. All the rapidly dividing cells are affected, particularly in the gastrointestinal tract and the immune system. Zinc-deficient children do get an immunoincompetence. It seems to be particularly a T-cell immunoincompetence. The children who come in with low zinc have increased infection, particularly of the mucosae—candidiasis of the mouth, the stomach, and so on—but they have all sorts of other deficits as well, and it is very difficult to sort out specifically one problem from another.

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