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Zinc Deficiency in Man: Its Origins and Effects [and Discussion]

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Zinc deficiency in man: its origins and effects

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The occurrence of zinc deficiency in man remained unsuspected until the 1960s. Since then, however, our understanding of the clinical importance of human zinc deficiency has grown rapidly. Zinc depletion has been demonstrated or suggested to be responsible for a variety of clinical features, ranging from minor aberrations of normal growth patterns and subtle impairments of taste perception to life-threatening disease states. The latter have been observed most frequently as a result of an inherited defect in zinc absorption and from feeding intravenously without adding zinc to the infusates. Notable clinical features of severe zinc deficiency states include a florid acro-orificial rash, behavioural changes, poor appetite, severe disturbance of normal growth and development, impaired reproductive performance, and frequent infections associated with abnormalities of the immune system. In general, the biochemical correlates of these clinical features remain poorly defined. While the clinical and laboratory diagnosis of severe zinc deficiency states is quite straightforward, existing techniques are inadequate for the detection of sub-optimal zinc nutrition. This difficulty presents a major challenge as there is evidence that mild or moderate zinc deficiency states are quite common in certain population groups. Though there is reason for particular concern about the zinc status of some socially deprived groups, inadequate zinc intake is also a potential problem in more affluent population groups. The occurrence of zinc deficiency is frequently associated with dietary factors that have an unfavourable effect on zinc absorption, for example phytate, and with a variety of special circumstances including premature delivery. There is evidence that the absorption of zinc from human milk is especially favourable. There is an outstanding need for further research to achieve a clearer understanding of the origins, incidence and effects of human zinc deficiency.

1. Introduction

The practical importance of human zinc nutrition and deficiency in health and disease is now well recognized. However, it was only about 20 years ago that the first abnormalities of human zinc metabolism were documented (Vallee *et al.* 1957) and since the occurrence of human zinc deficiency was hypothesized initially (Prasad *et al.* 1961). Before this, there is little evidence of interest in zinc nutrition in man, despite the well documented evidence of the economic importance of zinc deficiency in animal husbandry.

During the past decade there has been a rapid growth of interest and of applied research in human zinc deficiency. This paper will focus attention on progress achieved recently. These advances have made an important contribution not only to the growing awareness of the need for zinc in relation to human health, but to the status of the entire field of human trace element nutrition. However, our understanding of the origins and effects of zinc deficiency in man remains far from complete, and attention will also be directed to future research needs.

2. The effects of human zinc deficiency

(a) *Clinical*

A wide range of adverse effects of human deficiency has now been reported including most, if not all, of the features that have been observed in experimental zinc deficiency in animals For convenience, these features and their causes will be divided into those of acute severe and chronic mild, or moderate, zinc deficiency syndromes. However, this division is arbitrary. For example, though plasma zinc concentrations are usually very low (less than 6 μmol/l) in the 'severe' syndromes, the total body deficit in zinc may not be very great (Jackson 1977). It is quite possible that the body adapts to a low zinc status when this develops more gradually with depletion of certain body pools of zinc, for example in bone, while maintaining relatively high zinc concentrations in other tissues, for example blood. While this hypothesis is entirely speculative, the possibility that the extent to which different body pools of zinc are depleted is dependent on the aetiological circumstances does help to explain some otherwise puzzling variations in clinical presentation. Current knowledge of the changes in tissue and subcellular zinc concentrations and distribution and of adaptive alterations in metabolism and homoeostasis is extremely limited for human zinc deficiency states.

The occurrence of 'severe acute' zinc deficiency syndromes in man was not appreciated until Moynahan recognized the central role of zinc in the pathogenesis of acrodermatitis enteropathica (Moynahan 1973). The nature of the inherited molecular defect in this rare autosomal recessively inherited disease remains uncertain but it results in a partial block in the intestinal absorption of dietary zinc, and the phenotypic expression of acrodermatitis enteropathica can be attributed entirely to zinc deficiency (Moynahan 1974; Neldner & Hambidge 1975). The clinical manifestations develop first in early infancy, though these are usually delayed until after weaning if the infant is breast fed. Early features include skin lesions with a characteristic distribution, primarily adjacent to the body orifices and at the extremities (figure 1); stomatitis and glossitis; diarrhoea, which occurs in most cases and may be severe; depressed mood; growth failure and frequent infections. If untreated, there is typically a fluctuating but progressive deterioration involving anorexia, severe failure to thrive, alopecia including loss of the eyebrows, and recurring infections. Before the therapeutic value of zinc was recognized, there was frequently a fatal outcome in later infancy or early childhood. Some patients did, however, survive for long periods with no specific therapy or with treatment with human milk or diiodohydroxyquinoline. The empirical value of this drug was reported in the early 1950s and it is now known that it exerts its beneficial effects by enhancing zinc absorption. Acrodermatitis enteropathica is now treated by oral zinc therapy in quantities sufficient to overcome the partial block in intestinal absorption. The quantity required ranges from 30 to 50 mg Zn^{2+} per day, but may be considerably less during infancy. Zinc therapy results in a rapid, sustained and complete clinical and biochemical remission. A similar clinical presentation, with severe hypozincaemia and rapid response to zinc therapy, can result from acquired zinc deficiency, especially in patients maintained on prolonged intravenous feeding without adequate zinc supplements (Kay & Tasman-Jones 1975).

The skin lesions of severe zinc deficiency are typically acute erythematous vesiculo-bullous, and/or pustular. The rash may become generalized. Secondary infection is common, especially with staphylococci or monilia. In chronic stages, hyperkeratotic plaques may be present and the nails may become severely dystrophic (figure 2). Skin lesions are not usually evident in

more moderate chronic zinc deficiency, though a dry hyperkeratotic skin or acne may be observed. The one exception to this is in association with protein-energy malnutrition. In Jamaica the open sores associated with kwashiorkor appear to respond specifically to topical zinc therapy (Golden *et al.* 1980). The severity of the zinc deficiency necessary for the development of skin lesions may well be less in the presence of oedema and multi-nutritional deficiencies, and the distribution of these lesions is not identical to that of acrodermatitis enteropathica.

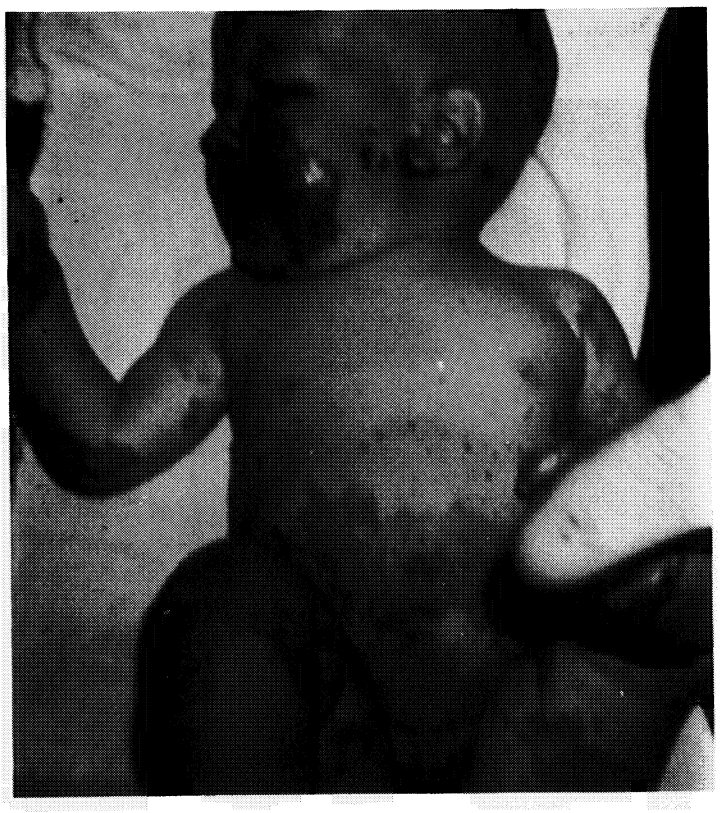

FIGURE 1. Acrodermatitis enteropathica: distribution of acute skin lesions. Reprinted by permission from Figure 1, page 84, chapter 7 in *Zinc and copper in clinical medicine* (ed. K. M. Hambidge & B. L. Nichols, Jr). Copyright 1978, Spectrum Publications Inc., New York.

Behavioural abnormalities are prominent in severe zinc deficiency (Walravens *et al.* 1978) and may also occur in less severe cases of zinc depletion. Irritability, lethargy and depression are evident even at an early stage in the clinical course. Improvement in hedonic tone and motivation to engage in the environment follow rapidly after the institution of zinc therapy. These observations indicate an important, but poorly defined, role for zinc in normal brain function, for which there is also evidence from other clinical observations (Henkin *et al.* 1975*a*). Intellectual capacity is, however, not impaired and there are no clinical data to support the practice of administering zinc in the management of learning disorders.

Other features of acrodermatitis enteropathica, which were observed particularly in prolonged survivors with incomplete remissions in the 'pre-zinc era', include hoarseness, blepharitis, conjunctivitis, photophobia and corneal opacities (Hambidge *et al.* 1977). Hypogonadism was observed in adolescence. The outcome of a very limited number of pregnancies in acrodermatitis enteropathica patients not treated with zinc suggests that human zinc deficiency is potentially teratogenic (Hambidge *et al.* 1975).

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Several of the features of acrodermatitis enteropathica occur in chronic 'mild' or 'moderate' zinc deficiency states. These include failure to achieve maximal physical growth potential, delayed sexual maturation, behavioural changes and poor appetite. Additional clinical features attributed to zinc deficiency include hypogeusia or dysgeusia (Henkin 1978), pica (Hambidge & Silverman 1973), impotence (Milham 1980), and delayed healing of wounds, ulcers and burns (Wacker 1978).

Impairment of physical growth is one of the most prominent and earliest detectable effects of zinc deficiency in the infant, child and adolescent. Dwarfism and delayed sexual maturation

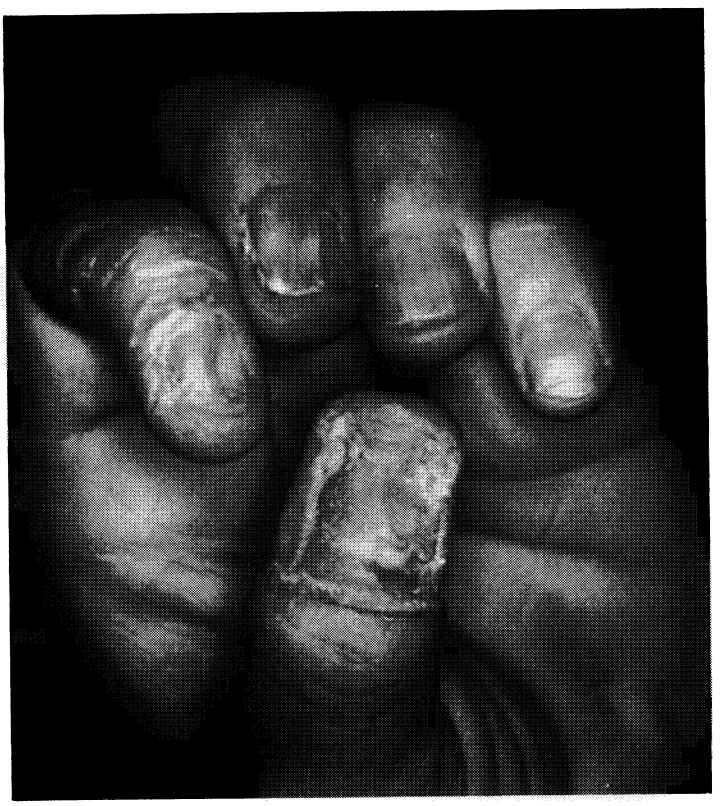

FIGURE 2. Acrodermatitis enteropathica: nail dystrophy.

are the cardinal features of the syndrome of adolescent nutritional dwarfism, an entity which has been observed in many geographical areas, particularly in developing countries. After the initial hypothesis of Prasad (1961), studies in Egypt and Iran have demonstrated that these features respond to zinc therapy with a period of 'catch-up' growth and sexual maturation (Halsted *et al.* 1972; Prasad 1978). The results of double-blind controlled studies of dietary zinc supplementation have indicated that mild zinc deficiency in otherwise normal infants (Walravens & Hambidge 1976) and young children (Hambidge & Walravens 1978) in the United States can be growth-limiting. Preliminary results from a study in progress (Walravens, Krebs & Hambidge, unpublished data) have provided further evidence that gains in height can result from dietary zinc supplementation of young children selected on the basis of low-height centiles and biochemical evidence suggestive of mild zinc deficiency. In each of the above studies, the effects of zinc supplementation on growth rate have been significant only in males. However, additional data are required to confirm a real, and unexplained, sex difference.

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Preliminary data from a study in progress (N. F. Krebs, unpublished data) have also demonstrated a significant increase in food intake in the zinc-supplemented, but not the control children. Though poor appetite has been noted frequently in association with mild zinc deficiency (Hambidge *et al.* 1972), other studies in Denver (Walravens & Hambidge 1976) did not reveal any increase in food intake in infants who were zinc-supplemented and grew more rapidly than controls. A correlation between height and weight deficits and low plasma zinc concentrations has been reported in school-aged children in Zagreb, Yugoslavia (Buzina *et al.* 1980) and in association with protein-energy malnutrition in Jamaica (Golden & Golden 1979).

Some cases of taste dysfunction are associated with low concentrations of zinc in plasma and parotid saliva (Henkin *et al.* 1975*c*). Treatment with zinc appears to be effective in some of these patients (Henkin *et al.* 1975*b*), but placebo has also proved useful (Henkin *et al.* 1976). Hypogeusia has been reported in association with evidence of zinc deficiency in cases of thermal burns (Cohen *et al.* 1973) in school-aged children in the United States (Hambidge *et al.* 1972) and Yugoslavia (Buzina *et al.* 1980), and in regional enteritis (McClain *et al.* 1980). Favourable responses to zinc supplementation have been noted (Hambidge *et al.* 1972), but further studies of selected subjects under adequately controlled conditions are needed to define the effects of zinc therapy.

(*b*) *Laboratory investigations*

Laboratory indices of zinc status will be discussed under diagnosis. This section will focus attention on other selected laboratory abnormalities that have been attributed to zinc deficiency in man.

Currently there is increasing interest in the role of zinc in the integrity of the immune system because of increased susceptibility to infection which is apparent in severe zinc deficiency and substantial evidence for the role of zinc in the immune system in experimental animals (Good *et al.* 1980). Cell-mediated immunity, determined by delayed cutaneous hypersensitivity responses and lymphocyte transformation studies *in vitro*, has been reported to be impaired in association with hypozincaemia and to improve after zinc therapy. This has been observed in acrodermatitis enteropathica (Chandra 1980), Down's syndrome (Björksten *et al.* 1980), obesity (Chandra & Kutty 1980), and in a malnourished young man (Pekarek *et al.* 1979). In general, these observations need further confirmation by controlled studies. Impairment of cell-mediated immunity in acrodermatitis enteropathica during relapse has not been a consistent finding in our experience or that of others (van Gool *et al.* 1976). The most persuasive evidence for impairment of delayed cutaneous hypersensitivity responses attributable to zinc deficiency has been provided by the effects of a controlled study of topical zinc application in patients suffering from protein-energy malnutrition in Jamaica (Golden *et al.* 1978). In the same population, thymic size has been reported to increase with zinc supplementation (Golden *et al.* 1977). Impairment of monocyte and neutrophil chemotaxis in acrodermatitis enteropathica has been found to be restored to normal as a result of zinc therapy *in vivo* and by pre-incubating the cells with zinc *in vitro* (Weston *et al.* 1977). These observations indicate that zinc has a specific role in leucocyte function. Similar beneficial effects of zinc therapy on chemotaxis have been reported for Down's syndrome (Björksten *et al.* 1980).

Before the recognition of the role of zinc in acrodermatitis enteropathica, abnormalities of fatty acid levels had been observed with sufficient frequency to support the hypothesis that the primary defect in this condition was a defect in the elongation–desaturation pathway of essential

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fatty acid metabolism (Neldner *et al.* 1974). However, there are problems associated with this hypothesis, including the lack of any detectable abnormalities in fatty acid metabolism in fibroblasts cultured from cases of acrodermatitis enteropathica and the finding of normal fatty acid levels in the blood of patients in clinical remission on diiodohydroxyquinoline therapy (Kayden & Cox 1973). These discrepancies can be explained if the observed abnormalities are all secondary to zinc deficiency (Hambidge *et al.* 1978*a*).

Zinc and vitamin A have at least two interactions in mammalian systems (Solomons & Russell 1980). Zinc deficiency may result in impaired synthesis of retinol-binding protein, leading to decreased release of hepatic stores of retinol into the blood. Zinc-responsive depression of serum vitamin A has been reported, for example, in protein-energy malnutrition (*Nutrition Reviews* 1980) and, though not consistently, in acrodermatitis enteropathica (Hambidge *et al.* 1978*b*). Retinol dehydrogenase is a zinc metalloenzyme, the activity of which is diminished in zinc-deficient animals. This enzyme catalyses the conversion of retinol to retinaldehyde in the retina, a necessary step for normal dark adaptation. Dark adaptation has been reported to improve with zinc supplementation in alcoholic cirrhotic patients who have failed to improve with vitamin A therapy alone (Morrison *et al.* 1978).

Other metabolic effects observed during the correction of zinc deficiency include improvement of nitrogen balance (Wolman *et al.* 1979); normalization of low serum cholesterol and triglyceride concentrations (Hambidge *et al.* 1978*b*); increases in circulating insulin with concurrent decreases in blood glucose (Wolman *et al.* 1979); and normalization of elevated blood ammonia (Prasad *et al.* 1978). There is evidence to indicate that membrane sodium transport is effected by zinc deficiency (Patrick *et al.* 1980).

3. Biochemical correlates of the effects of zinc deficiency

Zinc deficiency affects many tissues and organs including the central nervous, gastrointestinal, reproductive, skeletal and immune systems, epithelial tissues and the special senses of taste and vision. Metabolic disturbances include those of nitrogen, fat, carbohydrate, vitamins and minerals. These widespread effects of zinc deficiency are not particularly surprising in view of the many biological functions of this trace element. These functions have been elucidated most extensively with respect to enzyme systems. Each major enzyme classification includes at least one zinc metalloenzyme (Wacker 1978). Other functions possibly include a role in the structure and function of biological membranes (Chvapil 1976). Despite the many biological functions of zinc, direct correlations are few between disturbed biochemical indices and the clinical and metabolic sequelae of zinc deficiency in man. Many of the major features are thought to be attributable to impairment of nucleic acid metabolism and protein synthesis, which are known to be zinc-dependent at several crucial enzyme steps. These include: delayed physical growth, which, however, may also be secondary in part to anorexia; delayed wound healing; impairment of cell-mediated immunity; and abnormal foetal development. Direct evidence is limited, but depressed activity of deoxythimidine kinase has been reported in experimental zinc deficiency in man (Prasad *et al.* 1979).

Horrobin & Cunnane (1980) have suggested that many of the clinical effects of zinc deficiency are mediated through impairment of essential fatty acid metabolism and synthesis of the 1 and 2 series of prostaglandins. In support of this hypothesis, the effects of zinc deficiency in the pregnant rat have been shown to be similar to those of aspirin toxicity (O'Dell *et al.* 1977).

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Preliminary data from my laboratory suggest that levels of PGE_1, PGE_2 and $PGF_{2\alpha}$ in duodenal juices from acrodermatitis enteropathica patients are lower than normal (Casey, Walravens & Hambidge, unpublished data). However, experimental evidence in support of this hypothesis is limited and some of the similarities suggested (Horrobin & Cunnane 1980) between the effects of zinc and essential fatty acid deficiencies, for example the skin lesions, are somewhat tenuous.

Diarrhoea in zinc-deficient animals may result from alterations in membrane permeability; it is not typically associated with morphological changes in the intestinal mucosa, apart from abnormal inclusion bodies in the Paneth cells. Henkin (1978) has postulated that the abnormalities of taste perception are secondary to a decrease in the major zinc-containing protein in parotid saliva, termed 'gustin'. Gustin is thought to be necessary for the maintenance of the taste buds, and zinc may also be necessary for the preservation of the microtubular structures within the taste bud through which 'tastants' must pass to make contact with the sensory nerve fibres. Impaired activity of zinc metalloenzymes other than those involved in nucleic acid, protein and lipid metabolism may contribute to the clinical features of zinc deficiency. One example is a decrease in retinol reductase resulting in impaired dark adaptation but, as yet, there is little direct evidence for the clinical importance of other zinc enzyme defects. Finally, certain effects, for example impotence and abnormal carbohydrate metabolism, appear to be mediated through abnormalities of hormone synthesis or secretion.

4. The detection of human zinc deficiency

The combination of clinical features, especially the skin lesions, and severe hypozincaemia (figure 3) makes the detection of severe zinc deficiency in man relatively simple. Plasma zinc concentrations are usually less than 6 μmol/l and are frequently less than 3 μmol/l (normal 10–17 μmol/l). Though not essential for the diagnosis, additional laboratory indices of zinc status that are likely to be abnormally low include urine zinc excretion rates, erythrocyte and leucocyte zinc, skin zinc and serum alkaline phosphatase activity (Hambidge *et al.* 1978*b*).

Plasma zinc is also depressed in moderately severe degrees of chronic zinc deficiency, usually to a level between 6–9 μmol/l. Diagnosis is, however, considerably more difficult because the features are not specific and factors other than zinc deficiency, for example acute or chronic infection, can be associated with this degree of hypozincaemia. The difficulties in interpreting plasma zinc data are most apparent during pregnancy. Despite one recent observation to the contrary (Cavdar *et al.* 1980), the weight of evidence indicates that there is a decline in plasma zinc concentration during pregnancy of approximately 25% by the third trimester (Hambidge & Mauer 1978). However, the extent to which a decline can be accepted as normal at different steps of pregnancy has not been determined. This is an important practical problem because of the importance of zinc for normal foetal development and for normal parturition and because of evidence that human zinc deficiency can occur during pregnancy (Jameson 1976).

Detection of chronic mild zinc deficiency is particularly difficult. Clinical features, e.g. poor appetite and poor growth, are non-specific, and plasma zinc concentrations are frequently within the normal range. Hair zinc concentrations are very low (in contrast to severe zinc deficiency states in which hair growth is depressed), but results are difficult to interpret especially in the infant and young child in whom the diagnosis has to be considered most frequently. Currently, the only certain means of confirming the diagnosis is by means of a controlled trial of dietary zinc supplementation. This is a time-consuming and difficult procedure which is only

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applicable to population studies, but which is necessary to help clarify the circumstances, incidence and effects of chronic mild zinc deficiency.

Other techniques employed to assess zinc status primarily on a research basis include zinc balance studies and kinetic studies with zinc radioisotopes. Stable zinc isotope technology may soon be sufficiently advanced to provide a very useful research tool. The lack of a simple, reliable screening procedure for the detection of mild zinc deficiency remains, however, an outstanding problem.

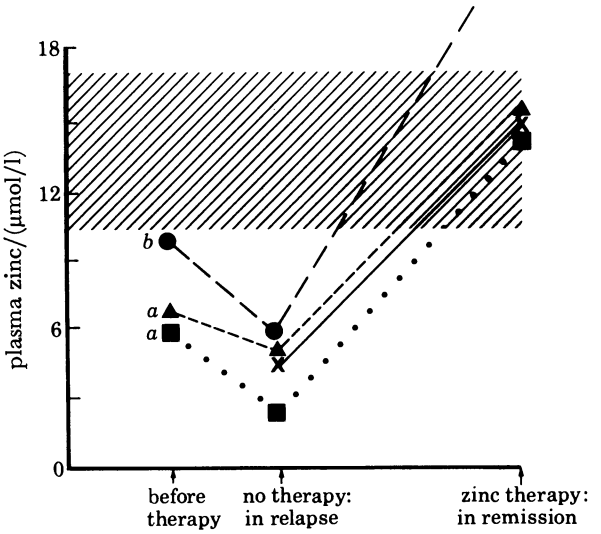

FIGURE 3. Plasma zinc concentrations of four cases of acrodermatitis enteropathica before and during zinc therapy. (*a*) Treatment with diiodohydroxyquin; (*b*) treatment with human milk. The shaded area shows the normal range.

5. CAUSES OF ZINC DEFICIENCY

Zinc deficiency in man may result from inadequate dietary intake, especially at times of relatively high requirement, for example during periods of rapid growth, and during pregnancy and lactation; dietary factors that have a deleterious effect on bioavailability; and defective transport of zinc across the brush border, which appears to be the site of impaired zinc metabolism in acrodermatitis enteropathica and may also occur with intestinal malabsorption syndromes, for example regional enteritis (McClain *et al.* 1980). Currently, conditions have not been identified in man that impair zinc transport across the mucosal cell or across the serosal membrane into the portal circulation. However, there remains a possibility that such circumstances may exist, for example in the interaction of trace elements at the level of intestinal metallothionein (Hall *et al.* 1979).

Zinc depletion may also be secondary to excessive losses, which can occur in a variety of disease states or unusual circumstances including excessive sweating, exudates and chronic blood loss. In the normal adult, daily losses of endogenous zinc approximate 0.5 mg each in sweat and urine and 1–2 mg in the faeces. Hyperzincuria occurs in a variety of disease states including alcoholic cirrhosis and other liver diseases, diabetes mellitus and sickle cell disease, and in association with muscle catabolism. Iatrogenic causes include the administration of chelating agents and diuretics. Excessive losses of zinc liganded to amino acids occur in patients receiving intravenous infusates of amino acids. Though these excessive losses are small

in relation to the body content they may deplete physiologically important body pools of zinc quite rapidly and, over a prolonged period, may cause a chronic zinc deficiency. Much greater losses of endogenous zinc have been recorded via the gastrointestinal tract in patients who have gastrointestinal disease that necessitates total intravenous nutrition and who continue to excrete excessive quantities of faeces or intestinal fluids (Wolman *et al.* 1979). These adults patient require, on average, 12 mg zinc intravenously per day to effect positive zinc balance compared with 2.5 mg per day if the mass of faeces is not excessive. The wide variation in zinc losses limits the value of any standard preparation for administration of zinc intravenously. Balance data are necessary to determine replacement requirements accurately.

Even in normal circumstances, large quantities of endogenous zinc are secreted into the lumen of the small intestine. For example, after a meal containing 2.4 mg zinc, 7.2 ± 2.0 mg zinc were recovered at the ligament of Treitz and 2.2 ± 0.6 mg in the distal jejunum from healthy adults (Matseshe *et al.* 1980). These observations illustrate the large quantities of endogenous zinc that have to be reabsorbed merely to achieve zero net absorption of this micronutrient. It is not known whether this endogenous zinc is absorbed preferentially.

Though excessive zinc losses occur in certain special circumstances, dietary factors are the major determinant of zinc status in the general population. These are of great practical interest because of the growing evidence that many people, even in affluent societies, may be at risk from sub-optimal intake of zinc.

The quantity of zinc ingested each day can vary widely depending on the food eaten. Some diets that are adequate in protein, calories and other nutrients can have a surprisingly low zinc content (Osis *et al.* 1972). There are a number of circumstances in which dietary zinc intake can be extremely low, for example in association with inadequate intakes of protein and calories (Canfield *et al.* 1980). The association between zinc deficiency and protein-energy malnutrition depends on geographical location, but it is apparent that zinc deficiency makes a significant contribution to the clinical presentation and rate of recovery in some countries. However, the severity of the zinc depletion depends not only on the absolute quantities of dietary zinc, but on the source. In Jamaica, zinc deficiency during recovery from protein-energy malnutrition is more severe when rehabilitation diets are based on soybean protein rather than cow's milk. The elderly and low-income groups may also be at increased risk from relatively low dietary zinc intakes.

An interesting example of an extremely low dietary zinc intake is provided by a recently recognized metabolic defect in which the lactating mother, despite an otherwise apparently normal zinc status, fails to secrete zinc from her mammary glands in normal quantities at any stage of lactation (A. Zimmerman, unpublished data). Though an inherited basis for this defect has not been proved, there are close similarities to the Lethal Milk mutation in mice (Piletz & Ganschow 1978). If these mothers breast-feed their infants, the typical features of acrodermatitis enteropathica develop at the age of 2–3 months. However, this occurs only if the infant happens to be delivered prematurely, which indicates that, even when zinc intake is exceptionally low, factors other than an 'absolute' deficiency of dietary zinc have a considerable role in dictating the outcome. The extremely low zinc intake (less than 0.5 mg per day for the first 6 months of post-natal life) of a breast-fed infant born at term to a mother who had defective mammary secretion of zinc, and who had previously had a severely affected premature infant, was not associated with hypozincaemia or any clinical evidence of zinc deficiency. This suggests that requirements for net absorption of zinc by term infants are considerably less than the

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values published by the World Health Organization (W.H.O. Expert Committee 1973) and is also one of several pieces of evidence in support of an unusually high bioavailability of zinc from human milk. In view of the probably adequate zinc status of this infant (despite the extremely low intake), it is reasonable to conclude that absorption of the breast milk zinc must have approached 100 %. Other evidence for a unique role of human milk in zinc absorption is discussed below.

In addition to this and other recorded examples of severe zinc deficiency in premature infants, there is considerable cause for concern that less dramatic degrees of zinc depletion may be common. Carefully conducted balance studies at University College Hospital, London (Dauncey *et al.* 1977) have revealed that premature infants of very low birth weight who were fed on pooled pasteurized human milk remained in negative zinc balance for an average of 2 months after delivery. During this period, the mean loss of zinc was 18 mg, which is comparable with the calculated total body zinc content of a foetus at 28 weeks of gestation (Widdowson *et al.* 1974). The foetus accumulates approximately 200 μg zinc per kilogram body weight per day *in utero* during the last 3 months of a full-term pregnancy (Shaw 1973). Though it may not be necessary for the premature infant to emulate intrauterine accumulation rates, it is reasonable to assume that positive zinc balance is desirable as soon as the premature infant starts to grow. Reasons for the poor zinc status of the premature infant may include immaturity of intestinal absorption mechanisms and inevitable losses secondary to the development of osteopenia. The latter is a common problem in infants of very low birth weight. It is not yet known if positive zinc balance can be achieved by increasing the dietary intake of zinc, nor has the optimal level of intake for the premature infant been established.

The variable effect of different individual food items and of composite meals on zinc absorption is by far the greatest single factor in determining whether any given quantity of dietary zinc beyond an absolute minimum will be adequate to maintain optimal zinc status. Of dietary constituents that are known to diminish bioavailability of zinc, phytate is the best known. The high phytate content of rural diets in Iran is probably the major cause of the zinc deficiency that appears to be endemic in that country (Reinhold *et al.* 1973). The high fibre content of the diet is also thought to make a major contribution to poor zinc absorption (Ismail-Beigi *et al.* 1977) in rural Iran, but no adverse effect of fibre on zinc absorption has been detected in studies in the United States (Sandstead *et al.* 1978). The effects may depend not only on the type of fibre but on other dietary constituents. The effects of phytate have been defined quantitatively in the rat by Davies & Olpin (1979) at the Rowett Research Institute. Dietary phytate:zinc molar ratios of not less than 15:1 in rats affect zinc status adversely, and these effects are not influenced by the absolute quantity of zinc in the diet. Davies & Reid (1979) have demonstrated that the phytate : zinc ratio in meat substitutes and meat-extenders made from soybean-based textured-vegetable protein range from 25:1 to 41:1. These products are being used increasingly as meat substitutes in human diets. However, the effect of soybean protein on zinc absorption in man has not been defined quantitatively as it has in the rat.

The complexities of this subject have been illustrated by the results of two recent studies by Sandström and coworkers (Sandström *et al.* 1980; Sandström & Cederblad 1980). Absorption of ^{65}Zn with a meal containing soybean protein (phytate: zinc molar ratio = 24:1) did not differ significantly from that with a meal containing chicken and beef (phytate:zinc = 3:1). The zinc contents of these meals were nearly the same. The effect of calcium in these studies appeared to be inconsistent. Absorption of ^{65}Zn with wholemeal bread was increased and with

soybeans was decreased in the presence of milk. Further studies are necessary, not only to define the quantitative effects of phytate, but also to determine the effect of calcium in the presence of phytate in human diets. The effects of several of the diets examined in these studies are difficult to assess because of variable quantities of zinc in the meals. However, variations of the zinc content did serve to demonstrate that absolute absorption, in contrast to percentage absorption, was correlated most closely with the zinc content of the diet. There was also a positive correlation between zinc absorption and the protein content of meals based on wholemeal bread with various combinations of milk, eggs, cheese and beef. However, one of the most outstanding results of these studies was the relatively low percentage absorption of ^{65}Zn even with animal protein. For different meals this ranged from 38 % down to 8 % with a mean of 18 % absorption. Only two meals, white bread and chicken, were associated with ^{65}Zn absorption greater than 30 % and the zinc content of these two meals was very low. These and other data (Molokhia *et al.* 1980; Pecoud *et al.* 1975; Oelshlegel & Brewer 1977) suggest that a wide variety of foods and composite meals have a marked inhibitory effect on zinc absorption.

Other trace elements, for example iron (Solomons & Jacob 1980), may also depress zinc absorption. The problem of potential interactions between different trace elements in infant dietary formulas is growing as a result of the current trend to supplement these formulas with relatively high concentrations of individual elements. While the questions posed by the adequacy of dietary zinc and dietary factors effecting absorption are of potential concern at all stages of the life cycle, there is no evidence to suggest that adults are at risk from zinc deficiency in 'normal' circumstances, with the exception of pregnant and lactating women, and probably, the elderly. In contrast, our experience in Denver suggests that the growing child is considerably more vulnerable and that sub-optimal zinc nutrition is most likely to begin during infancy. Therefore, factors that effect bioavailability of zinc from infant foods merit particular attention.

One individual case report has been cited already in support of an extraordinarily favourable bioavailability of zinc from human milk. Interest in this topic began with a recognition of the role of zinc in acrodermatitis enteropathica. Before this major advance, the beneficial effects of human milk in acrodermatitis enteropathica had been reported (Hambidge *et al.* 1977). The zinc content of normal milk after the first month of lactation is considerably lower than that of cow's milk (Hambidge 1976). This led to the concept that bioavailability of zinc from human milk was particularly favourable in this disease. Eckhert *et al.* (1977) hypothesized that this high bioavailability could be explained by a low molecular mass zinc-binding ligand (z.b.l.) that is present in human milk, but absent or difficult to detect in cow's milk. A similar z.b.l. was detected in rat milk and in the small intestinal mucosa of rats (Duncan & Hurley 1978). This latter z.b.l. is probably the same as the 'endogenous zinc chelator' described by Cousins (1979) and which appears to have a key function in transporting zinc across the intestinal epithelial cell to the basolateral membrane. Evans *et al.* (1975) have reported a similar or identical z.b.l. in pancreatic exocrine secretions, which is thought to facilitate the uptake of zinc across the brush border. Hurley *et al.* (1978) could not detect this z.b.l. in mucosal tissue of rats in early post-natal life, and proposed that the z.b.l. from the mother's milk had an important physiological role in zinc absorption in the young rat pup. The nature of this intriguing ligand has been the subject of considerable speculation and controversy (Lönnerdal *et al.* 1980; Evans & Johnson 1980). It is quite feasible, or even probable, that more than one ligand is involved. A defect in this ligand(s) could explain not only the impairment of zinc absorption in acrodermatitis enteropathica, but also the beneficial effects of human milk in that disease. Though there is

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preliminary evidence that the zinc-binding properties of the same or a similar z.b.l. are defective in the duodenal juice from patients with acrodermatitis enteropathica (Casey *et al.* 1979), there is also evidence that impaired uptake of zinc by the intestinal epithelial cells occurs *in vitro* in a system isolated from luminal contents (Atherton *et al.* 1979). The status of the endogenous chelator within these cells has not been determined, but excessive zinc does not accumulate within the intestinal epithelial cells (Hambidge *et al.* 1978*b*).

Though the beneficial effects of human milk at normal dietary levels of zinc may be attributable in part or primarily to this z.b.l., other properties of human milk may be important. The plasma reponse to a 25 mg zinc load administered to normal adults is very much higher when given in conjunction with human milk than with equivalent quantities of cow's milk or infant milk formulas based on either cow's milk or soybean protein (Casey *et al.* 1981). It is quite probable that, as with magnesium (Milla *et al.* 1979), the absorption of these relatively large quantities of zinc does not involve the same energy-dependent route that provides for the absorption of normal physiological quantities of dietary zinc. This speculation is based in part on the favourable response of acrodermatitis enteropathica to relatively modest oral zinc supplements. These results therefore suggest that there may be important, but possibly less specific, properties of human milk that exert a beneficial effect on zinc absorption even when the gut mucosa has matured. It is interesting to note that the plasma zinc response in these studies (Casey *et al.* 1981) was especially low when the zinc was administered in conjunction with selected synthetic or semi-synthetic infant formulas. This was an unexpected finding, which is not readily explained but which could have important practical implications as such diets are used increasingly in paediatric practice. Finally, it should be noted that there is already some evidence to indicate that the zinc status of breast-fed infants is superior to that of formula-fed infants, even when the formula contains a substantial zinc supplement (Hambidge *et al.* 1979). The development of adequate zinc stable isotope techniques in the near future may assist in determining more precisely the extent of zinc absorption from different milks and infant formulas.

6. Concluding remarks

During the past 20 years and especially during the 1970s, progress has been substantial in our understanding of the occurrence, effects and causes of zinc deficiency in man. The practical health-related importance of human zinc deficiency has now been recognized by many people concerned with human nutrition and health. However, this progress has also served to focus attention on the poorly understood aspects of zinc nutrition. These include the influence of the geochemical environment, agricultural practices and food processing procedures on the zinc content of cereals and other vegetable products. Quantitative data on factors influencing zinc bioavailability are needed urgently for the diets of infants and for those of children and adults, together with a clearer understanding of the physiology of zinc absorption from the intestine. Zinc metabolism in man requires extensive research, including the effects of various zinc deficiency states on zinc distribution and on homoeostatic and adaptive mechanisms. The effects of zinc deficiency in man cannot be understood adequately without clearer understanding of the biochemical and metabolic sequelae of zinc deficiency. Better laboratory techniques are required for the detection of mild, but probably quite common, zinc deficiency states in individuals and populations. Development of the optimal means of prevention and management of zinc deficiency states can be accomplished only after extensive interdisciplinary research in these and other areas.

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Discussion

J. K. Chesters (*Rowett Research Institute, Bucksburn, Aberdeen, U.K.*). Is loss of taste acuity useful in diagnosing zinc deficiency?

K. M. Hambidge. Though further confirmation is necessary, there is substantial evidence to indicate that zinc deficiency may lead to an impairment of taste perception. An association between impaired taste perception and zinc depletion has been reported in a variety of circumstances including idiopathic dysgeusia, thermal burns, hepatitis, regional enteritis, and in school-aged children in the United States and Yugoslavia. Hypogeusia is not, however, a consistent feature of human zinc deficiency, nor are all problems with taste perception related to disorders of zinc metabolism. Hence, measurements of taste perception, which are difficult and time-consuming, are not useful in diagnosing zinc deficiency.

M. J. Jackson (*Department of Human Metabolism, University College London School of Medicine, London, U.K.*). I was very interested in Dr Hambidge's technique of monitoring zinc absorption in man in which he has given an oral pharmacological dose of zinc (i.e. 25 mg) and followed the ensuing rise in plasma concentration. The data presented appear to demonstrate a difference between zinc absorption from human milk and cow's milk, but I must point out that the rise in plasma zinc that occurs with this technique is not only dependent upon the rate of zinc absorption but also on the rate at which zinc from the plasma is taken up by the tissues or excreted from the body.

I should also like to comment on the very interesting finding of a large secretion of zinc into the gastrointestinal tract during food ingestion in man. This may well provide an explanation for the well known depression of food intake seen in zinc-depleted animals. Thus a zinc-depleted animal may be unable or unwilling to ingest food because this will inevitably lead to a large secretion of zinc into the gastrointestinal tract that it then may be unable to reabsorb.

K. M. Hambidge. I agree completely that measurement of the plasma zinc response to an oral pharmacological dose of zinc does not provide an accurate measurement of zinc absorption. Radioisotopes of zinc cannot be used in our studies of infants and pregnant women, but techniques employing stable zinc isotopes may provide a satisfactory solution to this problem in the future. The studies referred to in the second comment were undertaken at the Mayo clinic by Dr Matseshe and his colleagues.

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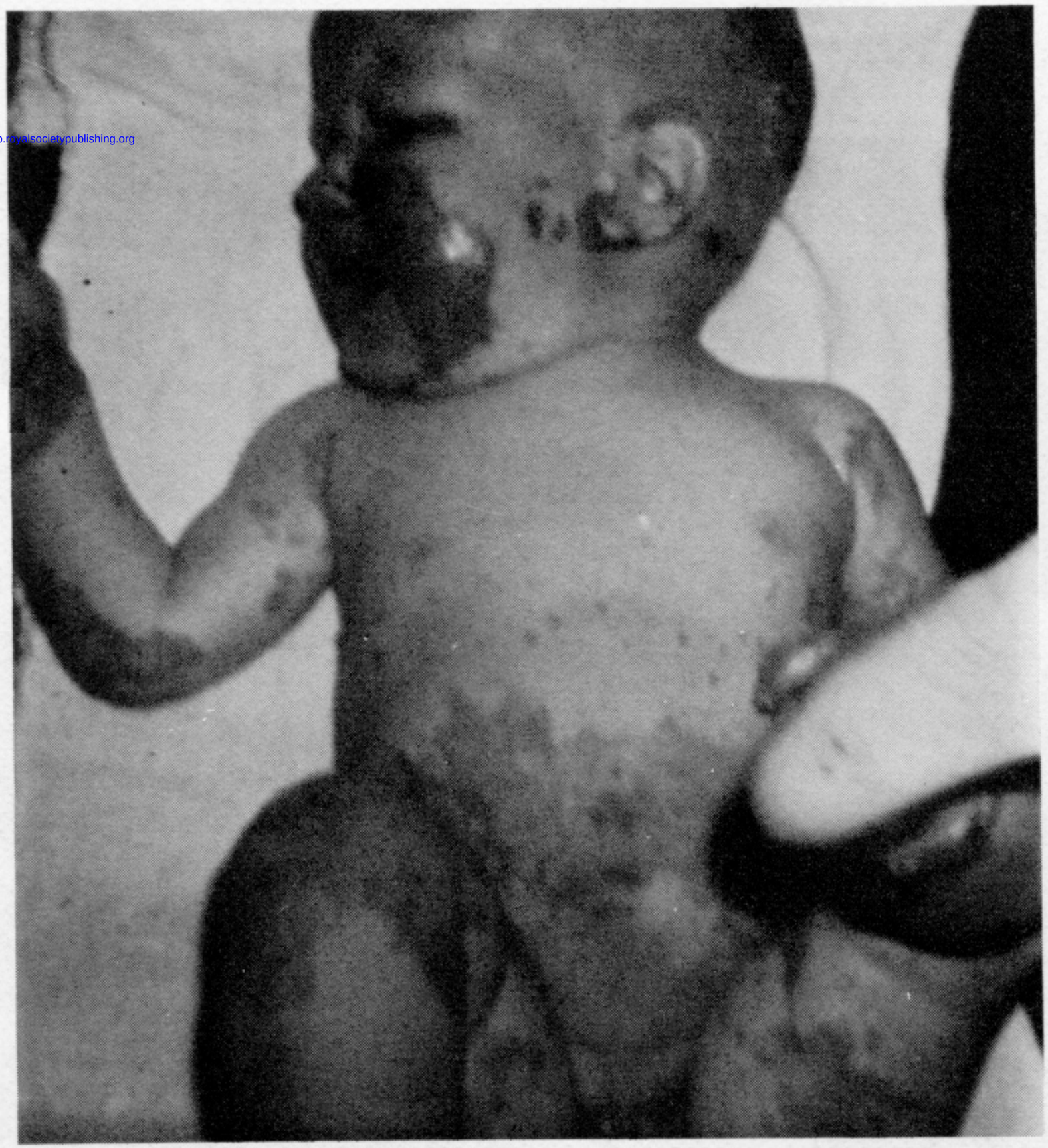

GURE 1. Acrodermatitis enteropathica: distribution of acute skin lesions. Reprinted by permission from Figure 1, page 84, chapter 7 in *Zinc and copper in clinical medicine* (ed. K. M. Hambidge & B. L. Nichols, Jr). Copyright 1978, Spectrum Publications Inc., New York.

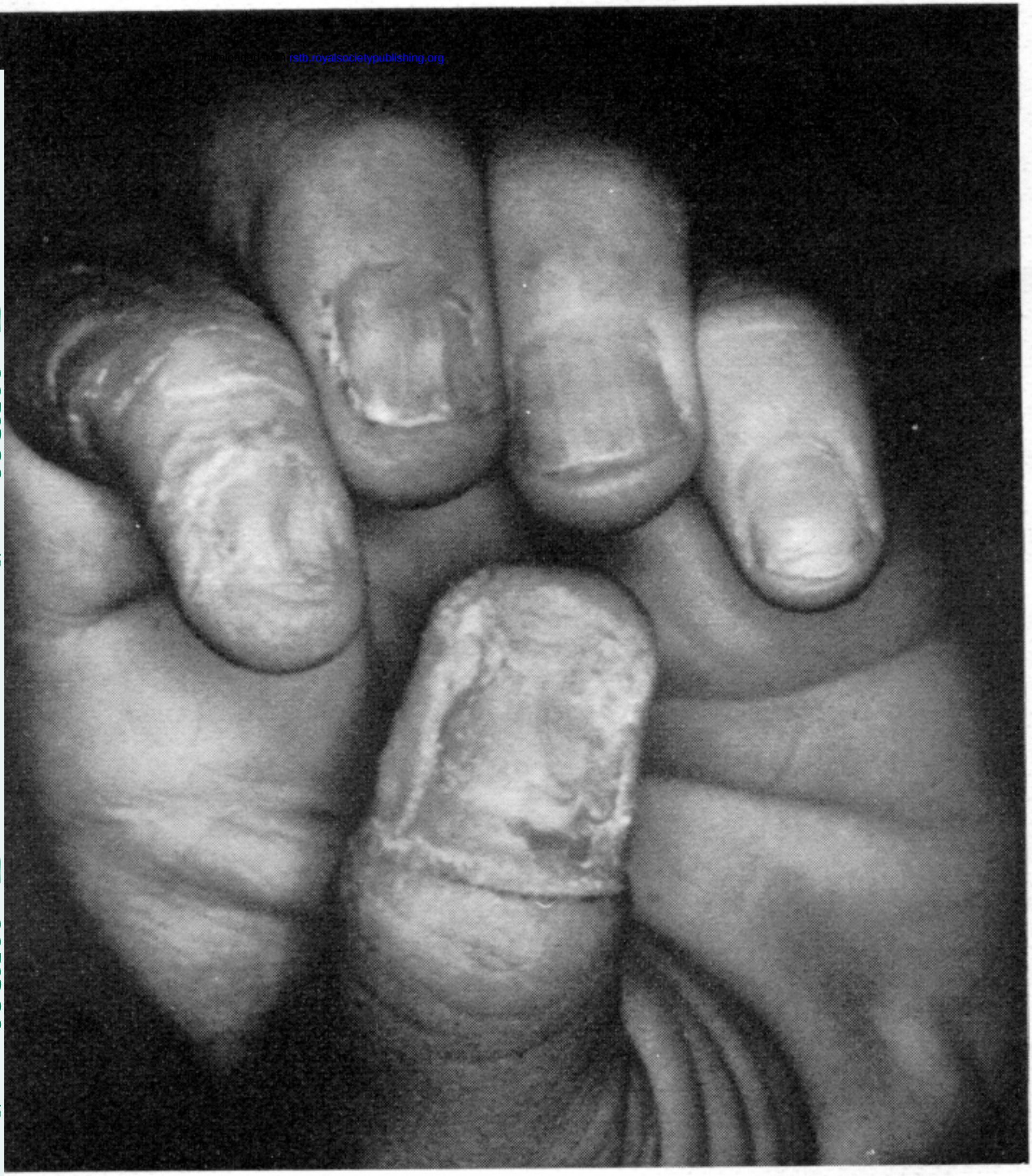

FIGURE 2. Acrodermatitis enteropathica: nail dystrophy.

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