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Recent Progress in Zinc Nutrition Research

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ABSTRACT

The importance of zinc as an essential nutrient in human nutrition has been emphasized by recent developments in research. Food consumption surveys reveal that hardly any age group in the United States consistently ingests the Recommended Dietary Allowances for zinc. The intestine, however, has specialized mechanisms to facilitate zinc uptake and to adjust its absorption to the nutritional requirements of the body. Moreover, a number of substances in foods reduce the biological availability of zinc. When individuals are exclusively dependent on intravenous feeding for their nutrition, specific quantities of zinc must be added to the nutrient solutions. Zinc has important interactions with other nutrients including iron, copper, essential fatty acids, vitamin C, and vitamin A. Zinc also plays a role in the immune defense systems of the body. A major deficiency in our present technology is a lack of suitable clinical indices for the accurate assessment of zinc nutriture in humans.

Eighteen abstracts relating to zinc nutrition were presented in 1970 at the meetings of the Federation of American Societies for Experimental Biology. In 1980, that number had increased to 66. With such burgeoning developments in zinc research, it is challenging to present a comprehensive update of the field. Thus, this review will concentrate on six areas in which substantive insights and conceptual advances have recently emerged: (1) customary consumption of dietary zinc by humans; (2) the intestinal regulation of zinc absorption; (3) interactions of zinc with other nutrients; (4) zinc requirements during total parenteral nutrition; (5) the clinical diagnostic assessment of zinc status in humans; and (6) the role of zinc in host defense and immune function.

CUSTOMARY CONSUMPTION OF DIETARY ZINC BY HUMANS

Since 1974, Recommended Dietary Allowances (RDAs) (1) have been established for zinc (Table 1). Reports from the United States, Finland,

and Chile have recently provided quantitative data on the content of zinc in human milk. Picciano and Guthrie (2) found a range of zinc content in 350 milk samples taken from 50 North American women between the 6th and 12th week postpartum to be 0.14–3.95 mg/liter, with a mean of 1.6 mg/liter. Vuori and Kuitunen (3) noted in Finnish women a decrease in zinc concentration from 4.0 mg/liter during the 2nd week of lactation to 0.48 mg/liter after 9 months of breast-feeding. Ruz et al. (4) in Chile found a mean concentration at 4, 8, and 12 weeks postpartum in 25 adequately nourished women to be 2.65, 1.66, and 1.60 mg/liter, respectively. There is substantial agreement among the three locations. If one uses a mean figure of 800 ml of breast milk as an estimate of daily intake, the various daily intakes by the infant who is exclusively breast-fed can be calculated. As shown in Table 2, except for the first month of life, the zinc intakes fall well short of the RDA recommendation. Stated another way, the density of zinc in human milk is generally insufficient to provide the recommended allowances of the mineral to infants. However, as the RDA for zinc is calculated on the basis of infant formulas, and, as zinc in breast milk may be more absorbable, breast milk still might provide sufficient zinc to meet the needs of infants.

Table 1. Recommended Dietary Allowances for Zinc (1)

Population	Age (yr)	Allowance (mg)
Infants	0.0–0.5	3
	0.5–1.0	5
Children	1–10	10
Males	11+	15
Females	11+	15
Pregnant	–	20
Lactating	–	25

In well-nourished Finnish women, Vuori et al. (5) found no correlation between customary intake of zinc and the zinc concentration in breast milk. A statistically significant reduction of zinc content was found in the milk of undernourished Chilean women at 3 months, compared with that of adequately nourished women (4). Whether or

Table 2. Daily Intakes of Zinc from Breast Milk at Various Ages[a]

Weeks of Lactation	*Ruz et al.* (4), Chile	*Vuori and Kuitunen* (3), Finland	*Picciano and Guthrie* (2), USA
2	–	3.00	–
4	1.99	1.58	–
6	–	1.88	↑
8	1.24	0.98	1.22[b]
12	1.20	0.66	↓
24	–	0.37	–
36	–	0.36	–

[a]Mg per day, assuming a daily intake of breast milk of 750 ml.
[b]Data from 6–12 weeks of lactation, all in one pool.

Table 3. Daily Intakes of Zinc from Customary Diets in Adults

Subject Population	Zinc Intake (mg)	RDA (%)	Description of Study
Diets for adults (5 diets, 15 meals)	9.4	63	Klevay et al. (7): various hospital diets in North Dakota
Adults, N = 22	8.6	57	Holden et al. (8): self-selected diets of middle-class adults in Maryland
Elderly adult males, N = 31	8.0	53	Greger (9): institutionalized elderly in Indiana
Elderly adult females, N = 34	8.6	57	
Elderly white males, N = 23	9.8	65	Greger & Sciscoe (10): elderly persons in an urban feeding program in Indiana
Elderly black males, N = 21	10.4	69	
Elderly white females, N = 26	9.9	66	
Elderly black females, N = 18	10.2	68	
Pregnant women, N = 29	11.0	55	Krebs et al. (11): middle-income women in Colorado
Pregnant women, 1st and 2nd trimester, N = 344	9.4	47	Hunt et al. (12): low-income Mexican-American women in California
Pregnant women, 2nd trimester, N = 279	10.0	50	
Lactating women, N = 40	11.4	46	Krebs et al. (11): middle-income women in Colorado

not dietary zinc supplementation to nursing mothers would substantially increase zinc output in breast milk has not been satisfactorily established. In contrast to the zinc content in breast milk, that of commercial infant formulas fed to children in Utah was 10.4 mg, exceeding the RDA (6).

Information on zinc consumption by adults has recently been available. Daily zinc intakes for various groups in various localities are presented in Table 3. Once again, it seems to be a question of zinc density in the diets. For lactating women to consume the requisite RDA intake of 25 mg of zinc daily from their accustomed diets, the subjects studied by Krebs et al. (11) in Colorado and those of Vuori et al. (5) in Finland would have had to eat a more zinc-dense diet (ingest 5000 kcal). Hence, based on the available survey data, a reasonable argument for dietary enrichment with zinc can be substantiated. This has been corroborated by evidence from Denver, Colorado, that dietary supplementation of infant formulas (13) and breakfast cereals (14) with zinc improved the zinc nutriture even of children from well-to-do middle-class homes.

REGULATION OF ZINC ABSORPTION

The intestinal absorption of calcium, magnesium, and iron appears to be regulated homeostatically; that is, raising of the dietary content reduces efficiency of absorption; on the other hand, at low dietary intakes, intestinal uptake is increased. Evidence in recent years has suggested that similar regulatory features are operative for zinc, and that specialized mechanisms govern the absorption of dietary zinc.

The Zinc-Binding Ligand

Over a decade ago, several investigators noted that zinc in the intestine was associated with a low-molecular-weight zinc-binding ligand (ZBL). The same ZBL was found in pancreatic secretions from dogs (15). Since it was also observed that pancreatic ligation of rats decreased the absorption of ^{65}Zn, Evans et al. (15) proposed that the ZBL might be a physiologically important factor in the normal absorption of dietary zinc in mammals. Over the ensuing years, a number of chemical entities have been proposed as candidates for the mammalian ZBL. It has been thought by different investigators to consist of amino acids (16), NNN'-trimethyl-1,2-ethanediamine (17), prostaglandin E_2 (18, 19), or a polypeptide (20). Recently, picolinic acid, a derivative of tryptophan metabolism, and citric acid have received the greatest attention.

A team of investigators led by Dr. Gary Evans at the United States Department of Agriculture laboratory in Grand Forks, North Dakota, has supported the notion that picolinic acid is the primary, functional ZBL in the intestinal lumen (21, 22). On the other hand, Hurley, Lönnerdal, and Stanislowski at the University of California have suggested that citrate is the chemical species physiologically important in intraluminal zinc-binding and uptake into mucosal cells (23, 24). A vigorous debate has raged between these two groups, hinging on disputes over the nature of chromatographic separation techniques and chemical analyses. In truth, among all of the compounds mentioned to date, none has unequivocally been shown to be the ZBL. Perhaps the perspective of Cousins and Smith (25) from Rutgers represents the most reasonable position. They have manipulated the zinc content by adding zinc to a sample of breast milk. They found that most of this added zinc was bound by substances of low molecular weight. This suggested to them that it was the lower content of proteins in breast milk that forced the zinc in human milk into an association with smaller molecules. They also submitted that the "spill-over" zinc combines with a heterogeneous variety of low-molecular-weight species that happens to be present in the fluid. Thus, a unique substance, responsible for 100% of the ZBL activity in the intestine or in breast milk, is unlikely to be found. Nonetheless, whether only one chemical or many constitute the ZBL will continue to be a question attracting the attention of investigators in mammalian biology for years to come.

The Role of Zinc-Binding Ligands in Breast Milk

Zinc-binding ligands secreted by the human mammary gland in breast milk appear to play a role in facilitating the absorption of dietary zinc by breast-fed infants. Johnson and Evans (26) demonstrated in the young rat that the zinc content of breast milk, among all human infant foods tested, had the highest biological availability, 46%. This report accompanies a number of other recent reports identifying a ZBL in human milk (23, 24, 27–31). Apparently, cow's milk has a lesser portion of its bound zinc associated with a ZBL fraction (29). As discussed above, the nature of the chemical identity of this ligand is still in dispute.

That the zinc from human breast milk is superior in insuring an adequate zinc nutriture in infants is suggested by observations in infants from middle-class families in Denver, Colorado, as reported by Hambidge et al. (32). He and his colleagues compared the plasma zinc concentration of three cohorts of infants at 6 months of age. One group had been fed a commercial formula with about 2 mg of zinc/liter; a second group, the same formula supplemented to about 6

mg of zinc/liter; and a third group was exclusively breast-fed. From the data presented in an earlier section, I would estimate the average zinc concentration in the breast milk over the course of the 6-month period to have been about 1.2 mg/liter. Nonetheless, the respective plasma zinc concentrations of the three groups of infants at 6 months of age were 70.7±1.8, 76.0±2.9, and 81.9±6.6 μg/dl (mean ± SEM).

The Role of Zinc-Binding Ligands in Acrodermatitis Enteropathica

A great deal has been learned about the behavior of zinc in human metabolism since the demonstration by Moynahan (33) that the clinical manifestations of acrodermatitis enteropathica (AE) (a severe skin and intestinal disorder in infants due to a metabolic error) were related to zinc deficiency, and by Lombeck et al. (34) that the pathogenesis of this zinc depletion in AE was zinc malabsorption. However, prior to the emergence of these insights, it has been noted that infants did not manifest this disorder while they were being breast-fed, and that a diet of breast milk could ameliorate the signs and symptoms of this disorder. With the detection of a ZBL in breast milk, an hypothesis was formulated that the etiology of zinc malabsorption in this disease might represent a defect in the endogenous ZBL system (22).

Workers in Denver, Colorado, aspirated samples of intestinal secretions from patients with AE and from healthy individuals. These fluids apparently did not exhibit a reduction in the amount of total binding ligand (35), but the affinity of the ZBL for binding zinc in the secretions of patients appeared to have been significantly diminished (36). As discussed, Evans has presented evidence for a ZBL role for picolinic acid. Krieger and Evans (37) studied a young child with AE who, prior to definitive diagnosis, had undergone an empirical therapeutic trial with pancreatic extract (Viokase). She responded to the Viokase, but was subsequently maintained on 60 mg of oral zinc daily. Chemical analysis of the pancreatic extract revealed a picolinic acid content of 3.4 μmoles (123 μg) per gram. This patient is now being maintained on a daily intake of 10 mg of zinc, 5 mg being provided from the diet and 5 mg being provided by a physiologic dose of zinc dipicolinate (38). Although this case study substantiates a high biologic availability for zinc from the picolinic acid salt, it does not prove unequivocally that picolinate is the endogenous ZBL defective in patients with AE.

Intracellular Transport and Regulation

As noted above, the entry of zinc into the body appears to be regulated at the level of the intestine. Using an isolated, perfused rat intestine, Smith and Cousins (39) have shown a marked difference in the transfer

of zinc from the lumen of the intestine to the blood, based on the previous diet of the animals. Intestines from rats on zinc-deficient diets took up more zinc than did those from zinc-supplemented animals. The subcellular mechanism for this regulation has also been partially elucidated by the group at Rutgers. Cousins and colleagues have shown that some of the zinc from an oral dose is bound to an intramucosal protein called metallothionein, and the zinc status of a rat or the amount of zinc in its diet appears to govern the induction of this protein (40, 41). This suggests a mucosal block theory, in which the zinc not required for the body's metabolism is trapped in the intestinal cells and denied passage into the bloodstream.

An interesting observation in human subjects tends to support the notion of regulation of zinc uptake by intestinal mechanisms under the influence of the diet. Dr. Freeland-Graves and coworkers at the University of Texas (42) performed zinc absorption tests in seven women who had been eating a mixed diet containing meat. She then placed these subjects for 3 weeks on a strict vegetarian diet with a high content of phytic acid. A repeat of the zinc absorption study after the period on the vegetarian regimen revealed a more avid uptake of zinc. This has been interpreted as suggesting that the intestinal mucosa of these women had made an adjustment to capture more of the zinc from the high phytate diet in which the bioavailability of the zinc would otherwise be greatly reduced.

The metallothionein proteins, however, may not only serve to reduce zinc absorption but also, under certain conditions, facilitate its absorption. This perspective comes from recent experiments published by Starcher et al. (43) in which they confirm the observations of Cousins on high intestinal concentrations of metallothioneins. Starcher and coworkers also demonstrated that, at the other end of the spectrum, that is, low intramucosal metallothionein contents, these proteins appear to favor the absorption of zinc. Thus, the fine control of mucosal transfer of dietary zinc, the full extent of participation by metallothionein, and the operation of this regulatory system in humans still await more detailed description.

INTERACTION OF ZINC WITH OTHER NUTRIENTS

It has been recognized for some time that a series of dietary binding or chelating agents—dietary fiber, phytates, inorganic phosphates, and tannins—will reduce the intestinal absorption of zinc. Recent research has extended our understanding of the interaction of zinc with other nutrients, not only in the intestine but also at the tissue level.

In terms of intestinal interaction, competition between zinc and iron and zinc and copper has recently been described. Investigators in Ontario, Canada, have shown that ratios of iron to zinc of from 2.5:1 to 10:1 will decrease the absorption of zinc in mice (44, 45). In the human intestine, a ratio of 2:1 or 3:1 of inorganic (nonheme) iron to zinc reduces the uptake of zinc (46). Heme iron, as would be derived from dietary consumption of meat and blood sausages, had no effect on zinc absorption in humans.

In short-term balance studies involving 12 elderly adults, an increase of dietary zinc consumption from 7.8 to 23.3 mg daily significantly reduced the retention of dietary copper (47). Fischer et al. (48) have localized the level of the zinc-copper interaction to competitive binding for a common intramucosal binding-protein of the metallothionein class. In their experiments with rats, a high-zinc diet reduced uptake and transfer of stable copper into inverted intestinal sacs in vitro.

Studies by Solomons et al. (49) failed to demonstrate either an inhibitory or a promoting effect of a range of doses of ascorbic acid from 0.5 to 2.0 g on the absorption of zinc in human subjects. McDonald and Margen (50) provided long-term balance data suggesting that the congeners of red wine enhance the absorption of zinc from the diet. In experimental animals, oxalates, which are potent inhibitors of iron absorption, did not affect the absorption of zinc (51).

At the tissue level, zinc interacts with a number of vitamins and other nutrients. Keltz et al. (52) found that the increment in dietary zinc from 11.0 to 19.5 mg daily produced a significant rise in urinary excretion of vitamin C and metabolites in young adult subjects. The nutritional significance of this finding remains to be elucidated. An interaction between zinc and vitamin A at two distinct anatomic levels has been identified. First, the enzyme responsible for the catalysis of the interconversion of vitamin A alcohol (retinol) to the vitamin A aldehyde (retinal) is an alcohol dehydrogenase. Mammalian alcohol dehydrogenases are zinc metalloenzymes, and the form of this enzyme found in the retinas of rats is zinc-dependent. Its activity can be reduced substantially by experimental zinc deficiency (53). In addition, zinc deficiency interferes with the transport of vitamin A out of the liver (54, 55). The major transport protein for hepatic vitamin A, retinol-binding protein, is thought to be sensitive to the zinc status of the organism (56). However, as protein deficiency and energy restriction can also reduce the synthesis or release of retinol-binding protein, the degree of influence exerted by zinc nutriture, per se, cannot be precisely determined.

Deficiencies of both zinc and essential fatty acids (EFA) result in

impaired growth and scaly skin rashes. In rats, the combined deficiency of zinc and EFA had a synergistic effect, aggravating the cutaneous signs and producing growth retardation (57). Feeding of an EFA-deficient ration to chicks reduced the manifestations of zinc deficiency (58). In both rats and chicks, the combined deficiency of zinc was associated with a high proportion of arachidonic acid in the fatty acids of the skin.

ZINC REQUIREMENTS DURING TOTAL PARENTERAL NUTRITION

The solution used for total parenteral nutrition (TPN) has a variable content of zinc, ranging from 0.02–4 mg/liter (59). In patients followed prospectively during TPN, an average decline in circulating zinc concentration of 4.9–6.6 μg/dl/week has been seen (60, 61). Clinical symptoms of zinc deficiency, including alopecia, skin lesions, diarrhea, immune deficiencies, behavioral disturbances, impaired taste acuity, and impaired wound healing, have developed during TPN in patients who were not receiving supplementation with zinc. The clinical manifestations responded to the administration of zinc.

Zinc balance studies recently conducted at the University of Toronto in 24 patients undergoing TPN treatment, reported by Wolman and colleagues (62), have contributed to our understanding of the nutritional requirements for zinc during TPN. Patients (three to four in each group) were assigned to receive amounts of parenteral zinc of 0.1, 2.5, 4.0, 7.0, 13.0, and 24.0 mg/day for each of three 1-week balance periods. In patients without diarrhea or small-bowel drainage, positive zinc balance was generally achieved with 2.5 mg zinc/day. In patients with gastrointestinal fluid loss, positive zinc balance required a daily infusion of 12.0 mg of zinc. Plasma zinc levels were positively correlated with the amount of zinc infused. During periods in which a patient was in positive zinc balance, nitrogen retention and insulin secretion were improved.

Based on an improved understanding of zinc metabolism and requirements, recommendations for parenteral administration of zinc during TPN have been made (63). The human fetus accumulates zinc at the rate of 250 μg/kg/day in the final trimester of pregnancy (64). An expert committee of the American Medical Association recommended that the premature infant receive a parenteral zinc dosage of 300 μg/kg/day (63), although, due to the variability of urinary excretion of zinc, many premature infants may require a larger dosage (65). For the full-term infant and for children up to 5 years of

age, the parenteral zinc requirement has been estimated to be 100 μg/kg/day. For stable individuals over 5 years of age, from 2.5 to 4.0 mg of zinc should be supplied daily during TPN. If the patient is in an acute catabolic state, zinc dosage should be increased to 4.5 to 6.0 mg. If TPN is indicated in a patient with substantial intestinal fluid loss, zinc requirements are greatly increased (62). In addition to the maintenance dose, 12.2 mg of zinc should be given to replace each liter of small-bowel fluid lost; 17.1 mg of zinc should be added for each kg of liquid stool or ileostomy fluid lost (Table 4).

Table 4. Recommended Daily Delivery of Zinc for Individuals Receiving Total Parenteral Nutrition

Population	Amount Recommended
Premature infants	300 μg/kg/day
Pediatric patients	100 μg/kg/day
Stable adults	2.5-4.0 mg/day
Adults in acute catabolic states	4.5-6.0 mg/day
Stable adults with intestinal losses	Add 12.2 mg for each liter of small bowel fluid and 17.1 mg for each liter of stool or ileostomy output

Until recently, no commercial preparation of sterile, pyrogen-free zinc was available. Zinc had to be prepared and added to solutions by individual hospital pharmacists. The FDA, however, has recently approved the marketing of such solutions of trace minerals, and zinc for TPN can now be purchased in ampules. Two biochemical determinations apparently assist the monitoring of zinc status during TPN. First, if one has a baseline concentration of circulating zinc, serial determinations serve as an index of the adequacy of the infused dosage. Moreover, a number of investigators report that a decline in the serum alkaline phosphatase often heralds the onset of zinc deficiency during TPN (66, 67). Excessively rapid administration of parenteral zinc can cause hypothermia, sweating, and blurred vision (68). Accidental administration of 22.7 mg of zinc/liter of infusion caused asymptomatic rises in serum amylase in seven patients (69).

ASSESSMENT OF ZINC STATUS

Hindering our understanding of zinc nutrition in humans is the lack of an unequivocal tool for the clinical assessment of total body zinc nutriture. An impressive array of tests and procedures has been used clinically or investigationally to determine zinc status (Table 5). The instruments include (1) measurements of zinc concentration in tissues and body fluids, (2) determination of zinc metalloenzymes or zinc-dependent proteins, (3) functional parameters, and (4) turnover and balance. The potential and pitfalls have been reviewed in detail elsewhere (59, 70).

The most widely used index of zinc status is the concentration of zinc, either in the serum or plasma. Under certain circumstances, for example, serial determinations made during TPN or in experimental zinc depletion, circulating zinc levels do reflect dynamic changes in zinc status. However, a number of factors, listed in Table 6, affect the validity of plasma or serum levels to determine zinc nutriture. Zinc determinations are subject to external contamination during extraction, transfer, storage and handling. Plastic syringes and zinc-free tubes should be used. As red cells contain 10 times the amount of zinc as does serum, hemolysis produces artifacts in zinc concentration. Ligation of the arms with a tourniquet while blood samples are being extracted raises zinc concentration (71). Prolonged fasting raises serum zinc (72). Endogenous or exogenous corticosteroids or estrogen hormones lower zinc concentration. Leukocytic endogenous mediator(s) (LEM), produced by phagocytic cells during inflammation or infection, mediates an internal redistribution of zinc from circulation to liver, transiently lowering zinc levels. Zinc concentration falls progressively following a meal; thus, blood samples taken while the individual is fasting are preferred. The absolute concentration of albumin can be a determinant of circulating zinc. Moreover, altered affinity of albumin for zinc can, in part, explain the depression of serum zinc levels of alcoholic cirrhotic patients (73). This altered affinity may also explain the rare instances of abnormal elevations in concentrations of circulating zinc, which may be related to changes in the affinity of serum proteins for zinc (74, 75). Zinc levels in hair have been used in an attempt to determine the average zinc status over a given interval. Normally, hair grows at the rate of about 1 cm/month. Traditional analytical methods for measuring hair zinc involve the digestion of the most proximal 1 to 2 cm of a whole *tuft* of hair cut close to the scalp. Hair zinc concentration varies with age. Moreover,

Table 5. Laboratory and Clinical Determinations Employed in the Assessment of Zinc Nutriture in Humans

Measurement of zinc concentration
In plasma
In red cells
In white cells
In hair
In saliva
In sweat
In skin
In fingernails
In urine (24-hr excretion)
Measurement of zinc metalloenzymes or zinc-dependent proteins
Serum alkaline phosphatase
Red cell carbonic anhydrase
Serum ribonuclease
Serum retinol-binding protein
Salivary gustin
Functional parameters
Dark adaptation of retina
Taste acuity threshold
White cell chemotaxis
Red cell ^{65}Zn uptake
Turnover and balance
Zinc balance (intake/output)
Zinc turnover and pool size (measured with radio- or stable isotopes)

shampoos, hair dyes, and rinses can contaminate hair with exogenous zinc. Various washing/rinsing procedures have been used among the various laboratories, but results obtained with different procedures are not comparable. Recently, nondestructive techniques involving anatomically and spatially oriented analyses have been developed in which proton-induced or electron-induced X-ray emission spectroscopy was used. In addition to zinc, these techniques can often provide simultaneous quantification of 20 to 50 elements in hair, and cross-sectional analysis of hair is also possible.

Advances in analytical methodology, however, portend a real possibility that stable, nonradioactive isotopes of zinc may soon become practical tools for the routine determination of pool size in the human body.

THE ROLE OF ZINC IN IMMUNE FUNCTION AND HOST DEFENSE

Zinc is also involved in the immune response. Several aspects of the role of zinc in immunity have been described. Gross et al. (86) found that rats that were fed zinc-deficient diets had depressed transformation of lymphocytes from the spleen, thymus, and peripheral blood in cell culture. The effects of zinc on other components of the cell-mediated immune response have been investigated. In rats (87) and mice (88, 89), T-cell helper function is depressed by ingestion of a zinc-deficient diet. In addition, zinc depletion of mice produced a significant increase in natural killer-cell activity of splenic cells (87).

Human zinc deficiency associated with acrodermatitis (90) or Down's syndrome (91) reduces the ability of the phagocytic white blood cells to move purposefully. The transformation of stimulated lymphocytes in cell culture and the ability of an individual to have a positive skin-test reaction are indices of cellular immunity. Zinc-deficient patients on TPN (92), with Down's syndrome (91), undergoing improper tube-feeding with a zinc-poor liquid formula (93) and with protein-energy malnutrition (94) showed a defect in one or both of these clinical measures of cell-mediated immunity. Zinc deficiency appears to have little effect on humoral immunity, that is, on antibodies. Zinc does seem to be involved, however, in the acute phase response to injury, a component of the host defense system by which the liver synthesizes acute phase proteins, such as ceruloplasmin and haptoglobin, at the onset of fever, infection, or inflammation. Part of the acute phase response entails the redistribution of zinc from the circulation to the liver. It has been suggested that this uptake of zinc in the liver facilitates the synthesis of these new proteins (95). The effects of a preexisting zinc deficiency on the acute phase response have not received concerted investigative attention.

CONCLUSIONS

The essentiality of zinc and its role in mammalian metabolism has moved to the forefront of nutritionists' consciousness in the past decade. RDA allowances have been set, but surveys have revealed that intakes generally fall below these levels; the biologic availability of zinc from certain foods is reduced; and its interaction with other minerals may limit its absorption under certain circumstances. On the other

hand, intestinal mechanisms to regulate zinc absorption, possibly honing it to the nutritional needs of the body, appear to be operative.

Zinc depletion does occur, usually in the face of disease or with improper administration of total parenteral nutrition, and the clinician should be alert to the implications of taste abnormalities, night blindness, and immune system dysfunction. Many more clinical consequences of zinc deficiency in humans may yet be recognized in the ensuing years.

The prevalent nutritional status of the majority of individuals in the United States and around the world is difficult to estimate. This stems, in part, from inadequacies in the traditional approach to diagnostic assessment of zinc nutriture, which relies heavily on determination of zinc levels in tissue and body fluids. Contemporary strategies aim at defining the physiologic and functional consequences of marginal zinc deficiency. A promising approach to nutritional assessment may be realized in the determination of total-body pool size by the use of stable isotopes of zinc.

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