INCAP Publication I-1160

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Factors affecting the bioavailability of zinc

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The task of nutrition researchers is to unravel further the mechanisms involved in the normal absorption of dietary zinc in human beings.

Zinc is a trace mineral nutrient essential to the growth and health of all mammals, including human beings. Its importance in a variety of clinical and environmental situations has been recognized (1). The Recommended Dietary Allowances (RDAs) (2) for zinc for different age groups and physiological states are shown in Table 1. They represent intake requirements to cover 97.5 percent of the *normal* population and assume the consumption of a typical American mixed diet (2). That customary intakes of zinc commonly fall short of the RDA ideal levels has been amply demonstrated (3-5). In addition to absolute dietary intakes, however, we have begun to understand that other factors intrinsic to the diet, or to the host, influence the *biological availability* of dietary zinc. Persons concerned with the adequacy of diets under different geographic, environmental, and clinical situations should become familiar with the latest findings regarding the factors affecting the bioavailability of zinc.

Normal physiology of zinc absorption

It is important to realize that the description of normal absorption is far from complete at the present time. For instance, the preferential location of zinc absorption in man has not been determined, but it is presumed to be in the upper jejunum (6). The stomach has no absorptive role (6). The degree to which the distal jejunum and ileum can absorb zinc that escapes quantitative absorption in the upper tract is uncertain. There seems to be an important *enteropancreatic* circulation of endogenous zinc.

The intestinal perfusion studies of Matseshe and his colleagues (6) at the Mayo Clinic have examined the change in intraluminal content of zinc attendant to the ingestion of a meal. For instance, when their subjects consumed a meal of steak, bread, and ice cream, containing 4.4 mg. zinc, the amount of zinc in the lower duodenum was 6.9 mg. Subsequently, the amount of zinc passing the proximal jejunum was 4.5 mg., and the chyme in the mid-jejunum contained 3.6 mg. zinc.

Thus, we should remember that each feeding represents for our intestine *two* meals; that is, not only do we receive ingested dietary zinc but also a roughly comparable influx of zinc enters the intestine from the meal-stimulated pancreatic secretions. Just as the nitrogen in pancreatic secretions must be recovered, so must much of the endogenous zinc in order to maintain normal balance of the nutrient.

The absorption of zinc is aided by a low-molecular-weight binding ligand, presumably of pancreatic origin (7). The mechanism of its action in facilitating zinc uptake is not entirely understood. Several groups of investigators working to identify the chemical nature of the zinc-binding ligand (ZBL) have offered evidence for different compounds being the natural ligand. Prostaglandins (8), citric acid (9,10), and picolinic acid (11-13) have each been proposed as the ZBL.

Zinc can be absorbed against a concentration gradient. It is taken by columnar epithelial cells of the mucosa. Detailed knowledge of the intracellular events has been elucidated in award-winning research from the laboratory of Robert Cousins of Rutgers University and has recently been reviewed (14). As shown in Figure 1, the zinc entering the enterocyte has three possible destinations: (a) It can pass through the basal or lateral membranes and enter the portal bloodstream. (b) It can enter the local, intracellular metabolic pathways of the absorbing cell itself. (c) It can become bound by a specific intracellular binding-protein rich in exposed sulfur amino acids—called metallothionein—and remain trapped and packaged within the cell, only to be returned to the lumen when the mucosal cell itself is sloughed by the intestine.

The fraction of ingested zinc which reaches the portal bloodstream is bound to a serum protein and carried to the liver for storage or processing and redistribution. The

Table 1. Recommended Dietary Allowances for zinc*

population	*age*	*allowance*
	yr.	*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

*Recommended daily intake based on the 1980 RDA (2).

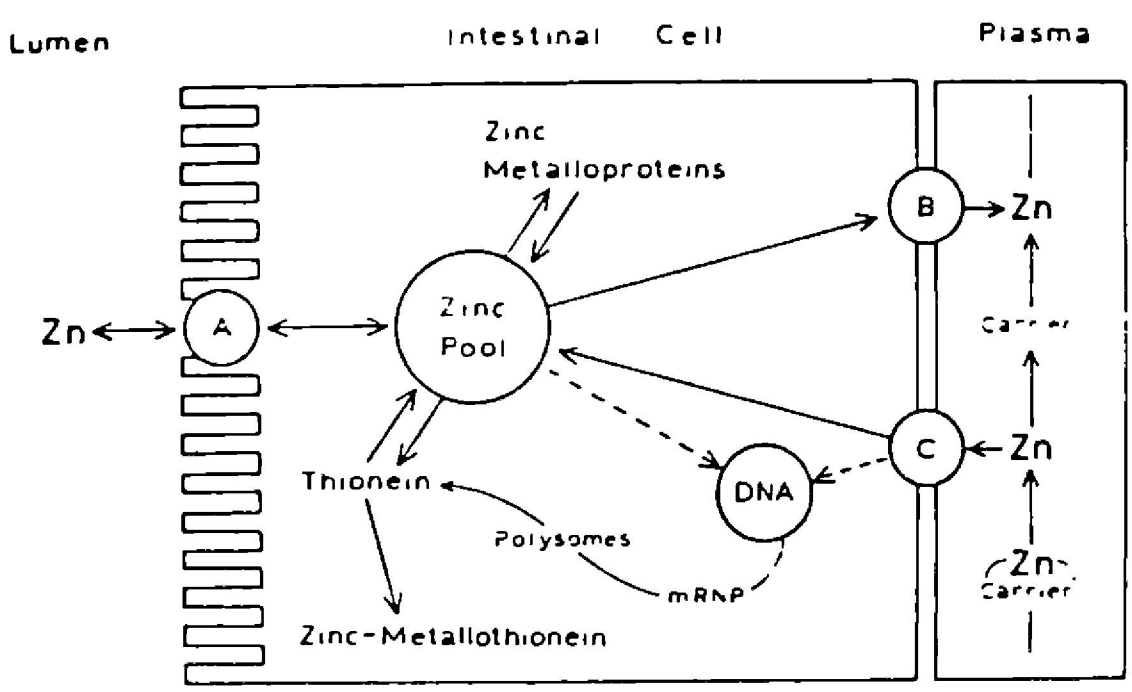

FIG. 1. *Intracellular pathways for zinc absorption from the intestinal lumen by intestinal mucosal cells. Source: Cousins (14). (Reproduced with permission.)*

transport-protein for newly absorbed zinc is either albumin, as proposed by Cousins (14), or transferrin, as proposed by Evans (15).

Host factors affecting zinc bioavailability

ROLE OF FEEDBACK REGULATION OF ZINC ABSORPTION. The intracellular events described by Cousins and associates, and illustrated in Figure 1, have implications for the regulation of zinc absorption; they suggest regulation of zinc uptake in accordance with the *nutritional* requirements of the host. It has long been appreciated that a servo-control mechanism operates for intestinal iron uptake (16) which (a) augments iron uptake by the body in the presence of depleted iron stores and (b) restricts the entrance of iron when total-body iron reserves are adequate. One of the viable hypotheses to explain this type of feedback regulation is the "mucosal block" theory. It postulates that unneeded mineral, although taken up by the enteric cells, will be withheld from passing into the body, while only the amounts needed to maintain normal balance or to reverse depletion will be permitted to enter the bloodstream.

Enhanced absorption of zinc by zinc-deficient animals has been demonstrated (17,18). It was also seen in zinc-deficient human subjects in Iran when they were placed on a diet of high zinc availability (19). When seven women volunteers who were ordinarily omnivorous in their dietary habits were abruptly switched to a high-fiber, high-phytate, lacto-ovo-vegetarian regimen, a more rapid velocity of zinc absorption was seen after only three weeks (20).

All of the aforementioned studies have been advanced as examples of homeostatic regulation. In studies conducted in Guatemala, the velocity of zinc absorption was elevated in children who received four weeks of supplementation with zinc (22.4 or 44.8 mg. elemental zinc per day) mixed into their diet.[1] When absorption studies were repeated at the completion of the trial, no zinc-related feedback reduction in absorption velocity was discernible with the dose, diet, and duration of our experiments. A need for tight regulatory control at the level of intestinal absorption is not so pressing since, unlike iron, which has a well-documented feedback control to avoid total-body overload, zinc has a number of accessible excretion routes. Nonetheless, the confluence of recent evidence suggests that enhanced absorption of zinc in zinc deficiency acts in concert with other mechanisms to maintain zinc homeostasis in man.

ROLE OF GASTROINTESTINAL DISEASE. Zinc deficiency is associated with a host of abnormalities of the digestive organs in experimental animals and in human beings. These are listed in Table 2. In gastrointestinal diseases, the immediate assumption is that any nutrient deficiency results from impaired uptake due to disruption of the absorptive process. However, other mechanisms, such as anorexia, mechanical obstruction, increased fecal or urinary loss of endogenous mineral, or decreased utilization, probably account for some of the observed zinc deficiency states in various digestive diseases. Nonetheless, reduction of effective absorptive surface due to *mucosal disease*, e.g., celiac sprue; *ablation*, e.g., short-bowel syndrome; or *exclusion*, e.g., jejunoileal bypass, can clearly cause zinc malabsorption in specific gastrointestinal conditions mentioned in Table 2. Zinc absorption

Table 2. Abnormal conditions of the digestive tract predisposing to zinc depletion in experimental animals or in man

geophagia
acrodermatitis enteropathica
celiac disease
short-bowel syndrome
jejuno-ileal bypass
diarrheal fluid loss
ileostomy fluid loss
protozoal infection
entero-colic fistula
pancreatico-cutaneous fistula
pancreatico-colic fistula
pancreatic insufficiency
cystic fibrosis

[1]Personal observations by the author.

tests in patients with jejunoileal bypass procedures for morbid obesity (21) and in patients with Crohn's disease (22) showed a reduced capacity to absorb zinc.

Furthermore, if the ZBL is indeed of pancreatic origin, pancreatic insufficiency would be expected to impair the efficiency of zinc absorption. Moreover, as dietary zinc of animal tissue origin is partly protein-bound, failure to digest dietary protein might compromise the release of zinc into a soluble form. Acute pancreatitis predisposes to zinc deficiency (23), but it is not established that this is related to malabsorption of dietary zinc. *Chronic* pancreatic insufficiency, on the other hand, does appear to reduce zinc absorption; fecal-balance studies in patients with cystic fibrosis revealed an apparent reduction in zinc absorption (24). This may explain the finding of marginal zinc nutriture or frank zinc depletion in some patients with cystic fibrosis (25-27).

THE ROLE OF ZINC-BINDING LIGAND. For years, the pathogenesis of an inborn error of metabolism called *acrodermatitis enteropathica* (AE) remained an enigma. This malady is characterized by hair loss, skin lesions, diarrhea, and maldigestion. Today, we recognize all of the hallmark manifestations of AE to be signs and symptoms of human zinc deficiency (28). Lombeck et al. (29) have conclusively shown that malabsorption of dietary zinc is the underlying cause of the zinc deficiency in AE. Evidence points to a defect in the production of ZBL as the basis of the zinc malabsorption in AE. The only effective therapy, prior to the advent of zinc supplementation, had been the administration of the antiprotozoal agent, diodoquin. A chelator of zinc, diodoquin may have been partially compensating for the loss of effective natural ZBL activity in the intestine. Researchers in Denver have reported a qualitative defect in binding affinity of the ZBL-containing fraction of human pancreatic secretions in patients with AE (30). Thus, it appears that qualitative or quantitative defects in human ZBL production in an individual can predispose to zinc malabsorption.

Dietary factors

Dietary factors influence the absorption of zinc. These include "extrinsic" factors, that is, other chemical components of the diet that may inhibit or enhance zinc absorption, and "intrinsic" factors, related to the chemical nature of the zinc itself, which may increase or decrease its biological availability.

EXTRINSIC FACTORS

Dietary substances inhibiting zinc bioavailability. Over a decade ago, it was demonstrated that the whole-grain, unleavened, wheaten bread, *Tanok*, the staple of the rural Iranian diet, markedly reduced the absorption of dietary zinc (31). The flat breads consumed by the urban population in Iran had a substantial, but lesser, inhibitory effect of zinc absorption (32). More recently, we have shown a dramatic inhibition of zinc absorption by constituents of the traditional Guatemalan diet, corn tortillas and black beans (33,34). Dark bread interfered more than white bread with the absorption of zinc in studies by Pecoud et al. (35).

The dietary factors responsible for impaired zinc absorption in these whole-grain or leguminous foods have been identified. The most important factor appears to be dietary fiber (32,36). The phytic acid in these foods also appears to inhibit zinc absorption in animals and in human beings (35,37-41). The strict influence of the phytate/Zn molar ratio is debated, however. Davies and Reid (38) found that they could accurately predict the phytate/Zn ratio of a food from its effect on the weight-gain of rats. Morris and Ellis (40) found that the dietary level of calcium and the total delivery of zinc by the diet modulate the effect of phytate on zinc absorption. Reducing the phytate content of wheat bran improved zinc availability (41). Thus, despite a comparable *content* of zinc in whole grains and in red meats, the fiber and phytins of the grains reduce considerably the biological availability of their intrinsic zinc. Other common foods in the modern Western diet with demonstrable inhibitory effects on zinc absorption are cow's milk, cheese, coffee, eggs, celery, and lemon (35,42).

An inhibitory interaction between zinc and various chemical constituents of the diet has also been demonstrated. Copper and zinc compete for absorption by the intestine (43). However, the rarity of an excess of copper over zinc in a regular diet gives this interaction little real nutritional significance.

A situation of considerably greater importance is a competitive interaction between nonheme (inorganic) iron and zinc. Recent studies in our laboratories have demonstrated a significant reduction in zinc absorption in the presence of a 2:1 or 3:1 ratio of nonheme iron to zinc (Table 3). Heme iron, that is the iron in the porphyrin ring of hemoglobin, had no effect on zinc absorption (Table 3). Since the RDA for zinc in the first six months of life is 3 mg.—whereas that for iron is 10 mg.—if an infant formula is formulated to these specifications, the resulting Fe:Zn ratio will be 3.33:1. According to our findings, this is apparently sufficient to reduce the efficiency of zinc absorption by a significant degree (44).

High doses of ethylenediaminetetraacetic acid (EDTA), in molar ratios of EDTA:Zn of 0.76:1 and 2.2:1, have been shown to reduce the absorption of zinc from aqueous solutions in adult subjects (33). Lower EDTA:Zn ratios had no significant effects. On the other hand, within certain EDTA:Zn ratios, adding EDTA to the diets of experimental animals has actually increased the biological availability of zinc (45). Whether this effect will be observed in the diets of human beings awaits further investigation. Ascorbic acid and oxalic acid apparently have no inhibitory effects on dietary zinc absorption (46,47).

Dietary substances enhancing zinc absorption. Except for the unique case of a ZBL in breast milk discussed later in this article, conclusive demonstration of dietary component(s) enhancing the absorption of dietary zinc is lacking. Ascorbic acid, which markedly increases the biological availability of inorganic iron, has no similar effect on zinc (46). A slight, but not statis-

Table 3. Zinc: iron interaction in the human intestine

group	treatment*	no. of subjects	Fe:Zn ratio	Δ plasma Zn, μg./dl.†			
				1 hr.	2 hr.	3 hr.	4 hr.
I.	25 mg. Zn^{++} alone	8	0	56±11	85±18	72±16	48±12
II.	25 mg. Fe^{++} + 25 mg. Zn^{++}	7	1:1	18±8‡	40±9	47±8	36±9
III.	50 mg. Fe^{++} + 25 mg. Zn^{++}	7	2:1	23±2‡	44±4‡	38±8	27±8
IV.	75 mg. Fe^{++} + 25 mg. Zn^{++}	7	3:1	16±3‡	27±5‡	21±4‡	19±4‡
V.	75 mg. heme iron + 25 mg. Zn^{++}	5	3:1	59±14	70±21	58±23	44±14

*Minerals dissolved in 100 ml. of Coca Cola®.
†Rise above fasting plasma zinc level (mean±S.E.).
‡Statistically significant difference of at least $p \leq 0.05$ from corresponding change with treatment I.

tically significant, enhancement in the rate of zinc absorption was produced in normal volunteers by the simultaneous administration of two amino acids, histidine and glutamine (42). McDonald and Margen (48) demonstrated increased dietary zinc uptake in subjects consuming red wine or dealcoholized red wine, suggesting enhancing properties of the congeners. Evidence in experimental animals suggests that addition of lactose to feed increases zinc bioavailability (49). More research into the potential of specific food constituents to enhance the bioavailability of dietary zinc in the human alimentary system is needed.

INTRINSIC FACTORS

Zinc bioavailability from foods of plant and animal origin. Knowledge about the chemical form of zinc in foods is far from complete. In oysters, the most zinc-rich of all foods consumed by human beings, studies have shown that about half of the zinc is loosely bound (50,51). Much of the remainder, however, seems to be specifically incorporated into zinc-containing enzymes (51). Since the zinc content of plants reflects the zinc content of the soil, it is likely that zinc in vegetables and cereals is in a primarily inorganic form. O'Dell et al. (52) observed a greater biological availability of zinc to rats fed a diet based on food of animal origin than to rats fed a diet based on vegetable matter. The studies of Matseshe et al. (6) would also suggest at least a more rapid removal of zinc from the intestinal lumen after a meal of beef than after one of cereal. On the other hand, rats fed corn hydroponically labeled with ^{65}Zn absorbed *more* radioisotope from this diet than they did from a comparable diet based on cooked liver, bio-organically-labeled with ^{65}Zn (53). Similarly, dietary zinc of lyophilyzed oysters appeared to have no advantage over zinc carbonate as a source of dietary zinc when equal amounts were added to rat chow (54).

We have undertaken a series of studies feeding raw oysters as the source of zinc to human subjects to examine the question of whether absorption of "organic" zinc differs from that of "inorganic" zinc (34,44). The oysters contained 0.9 mg zinc per gram, and a substantial rise in plasma zinc concentration was observed when either 60 or 120 gm. of oysters was consumed alone (Figure 2).

As discussed earlier, the components of the Guatemalan diet inhibit the absorption of zinc. To address the issue under consideration, 120 gm. of oysters, containing 108 mg. zinc, were fed alone or with 120 gm. of black beans or 120 gm. of corn tortillas (Figure 3). The progressive reduction in the rise of plasma zinc is clearly demonstrated. Subsequently, when the same amount of zinc as zinc sulfate was mixed into the beans or tortillas, essentially identical plasma zinc curves were obtained (34). This suggested to us that the bioavailability of organic and inorganic zinc was the same (34).

Subsequently, however, we compared the effects of inorganic, nonheme iron—in a 2:1 Fe:Zn ratio—on the absorption of oyster zinc. In companion experiments, a clear inhibition of zinc absorption had been seen at the 2:1 Fe:Zn ratio when zinc sulfate was the source of the zinc (44). However, as shown in Figure 4, the addition of the same ratio of iron (as ferrous sulfate) to an oyster meal had no effect on zinc absorption.

It is apparent, then, that some inhibitors of zinc absorption, namely the phytates and fiber in legumes and whole grains, have an equivalent inhibitory effect whether the zinc is from an "organic" or an "inorganic" source. On the other hand, another inhibitor of zinc uptake, nonheme iron, had distinct effects depending upon whether the source of zinc was a salt or the flesh of oysters. This suggests to us the hypothesis (44) that the zinc in animal tissue is protected from certain types of inhibitors of zinc absorption, namely those which are competitive inhibitors, i.e. iron or copper, but not from the potent binders and chelators such as fiber.

Zinc absorption from breast milk. Evidence from several types of observations suggests strongly that the zinc in breast milk is more biologically available than the zinc in bovine milk. For instance, it has long been known that acrodermatitis enteropathica manifestations rarely appear while the affected child is being breast fed and that a breast milk diet can ameliorate the signs and symptons of AE. Johnson and Evans (55) reported that ^{65}Zn absorption in intact rats was greater from human milk than from cow's milk or from a host of representative infant formulas. Rats absorbed an average of 59 percent of the zinc from human milk. Moreover, a series of reports has demonstrated that the intrinsic zinc in breast milk is secreted in association with a low-molecular-weight binding ligand, indistinguishable from the ZBL isolated from intestinal secretions (10,56-58). As the concentration of zinc, *per se*, in breast milk is on the order of 0.5 to 3 mg. per liter, the adaptive significance of increased biological availability is easily appreciated.

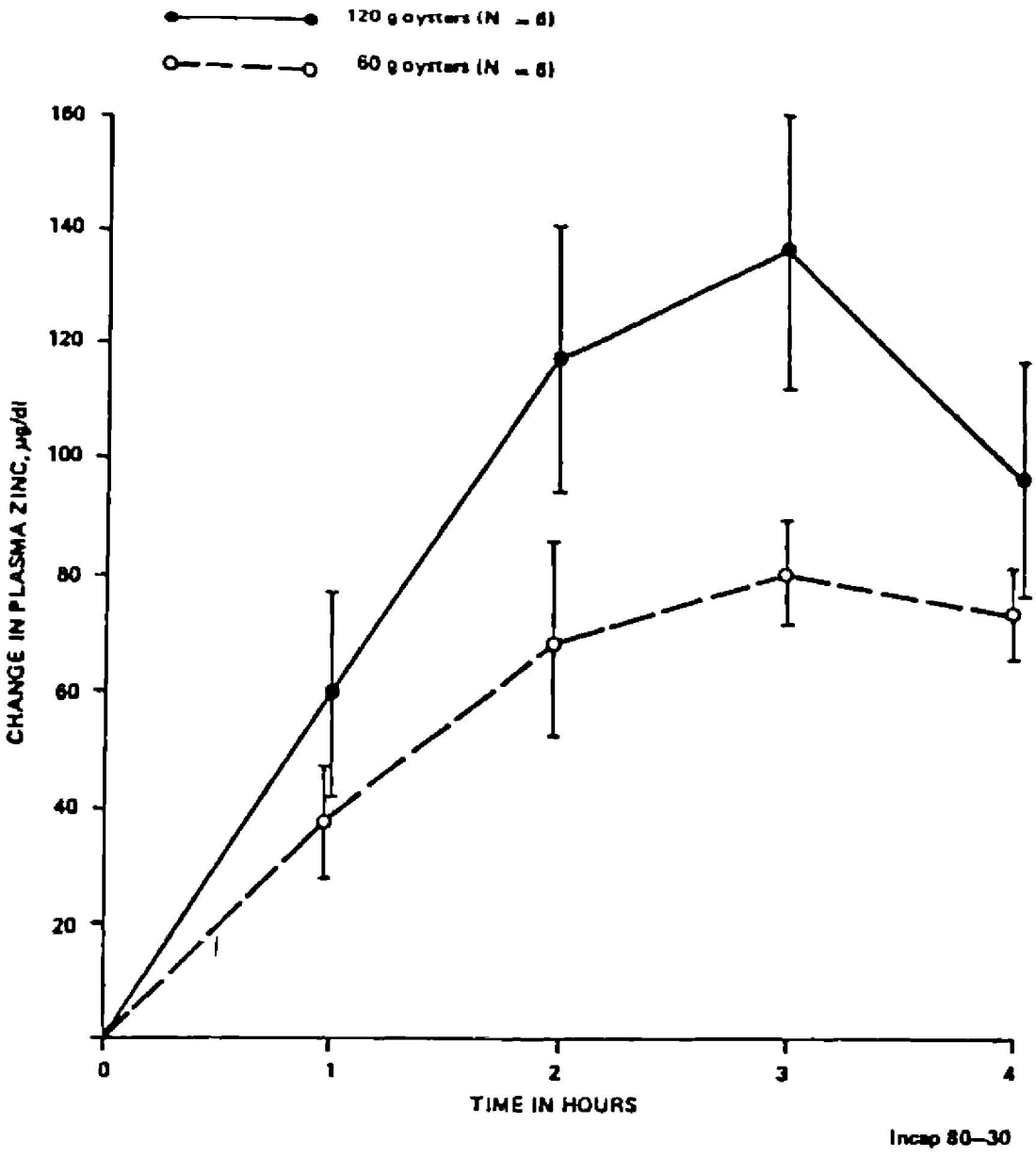

FIG. 2. *Changes in plasma zinc concentration (mean ± SEM) at four 60-minute intervals following the ingestion of 60 gm. (dotted line, N = 6) or 120 gm. (solid line, N = 5) of raw oysters by normal subjects.*

Frontiers in zinc bioavailability research

The door has only been pushed ajar with regard to unlocking the knowledge on zinc bioavailability in the human being. Very recent technological advances may accelerate the progress of human experimentation, however. These include the ability to reduce substantially the dose of ^{65}Zn necessary for detection in man with modern, ultrasensitive whole-body counting instrumentation (59). Moreover, the use of a zinc radioisotope of short radioactive half-life ^{69m}Zn, which provides much lower duration of radiation exposure than ^{65}Zn, has been introduced into nutritional research (60,61).

Perhaps the most promising of all technological innovations, however, has been the introduction of stable (nonradioactive) isotopes of zinc as tracers in human zinc-absorption studies (62,63). Natural zinc is a mixture of five discrete and distinct isotopes, occurring in fixed, immutable proportions in nature. Sensitive methodology for the quantitative determination of stable isotopes is available both with mass spectrometry and with neutron activation analysis procedures. Thus, by enriching a meal or diet with a known amount of a given stable isotope of relatively low abundance—such as ^{70}Zn or ^{68}Zn—and measuring the change in specific abundance in stools, a reliable and safe estimation of intestinal removal of zinc can be achieved. The same stable isotopes of zinc can also be measured in blood and plasma after single-dose administration or in red cells or other tissue after chronic dosing with stable zinc.

Thus, for subjects such as infants and children, or pregnant or lactating mothers, individuals in whom elective, experimental administration of radioisotopes

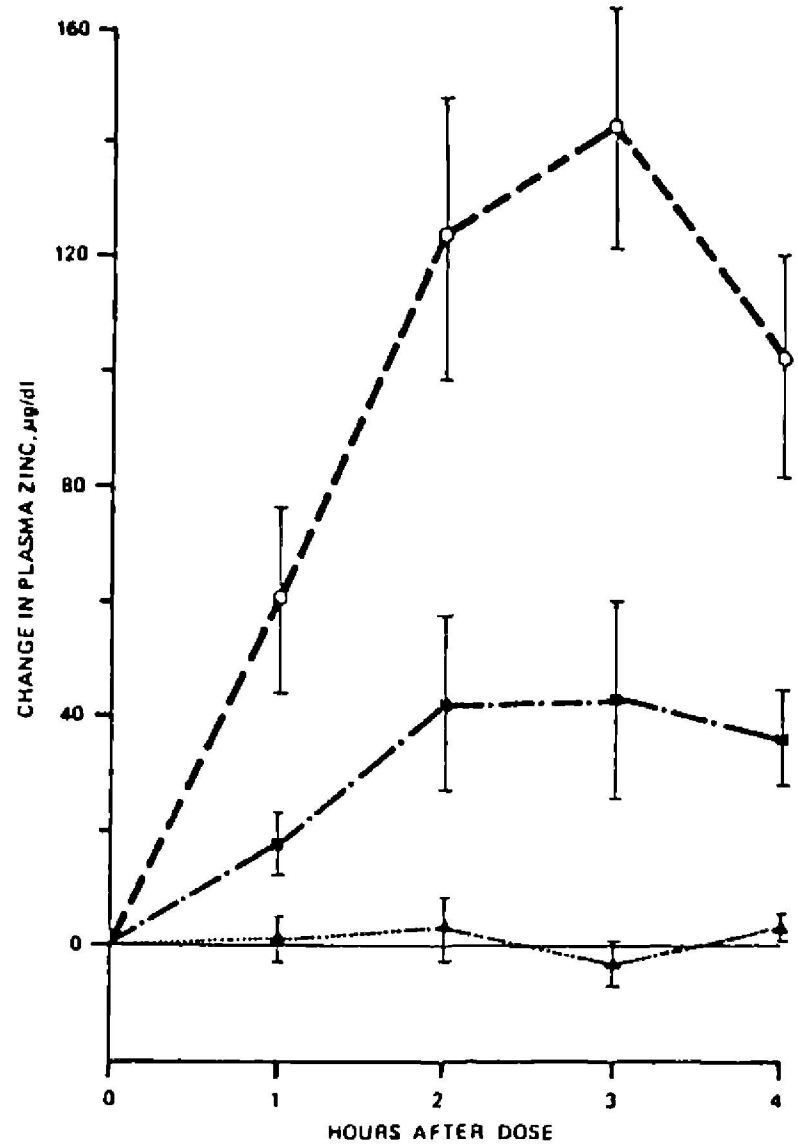

FIG. 3. *Changes in plasma zinc concentration (mean ± SEM) at 60-minute intervals over four hours following ingestion of 120 gm. of oysters containing 108 mg. elemental zinc. The oysters were consumed alone (dashed line, N = 6); with 120 gm. of black bean gruel (dashed and dotted line, N = 5); or with 120 gm. of corn tortillas (dotted line, N = 4). Source: Solomons et al. (34).*

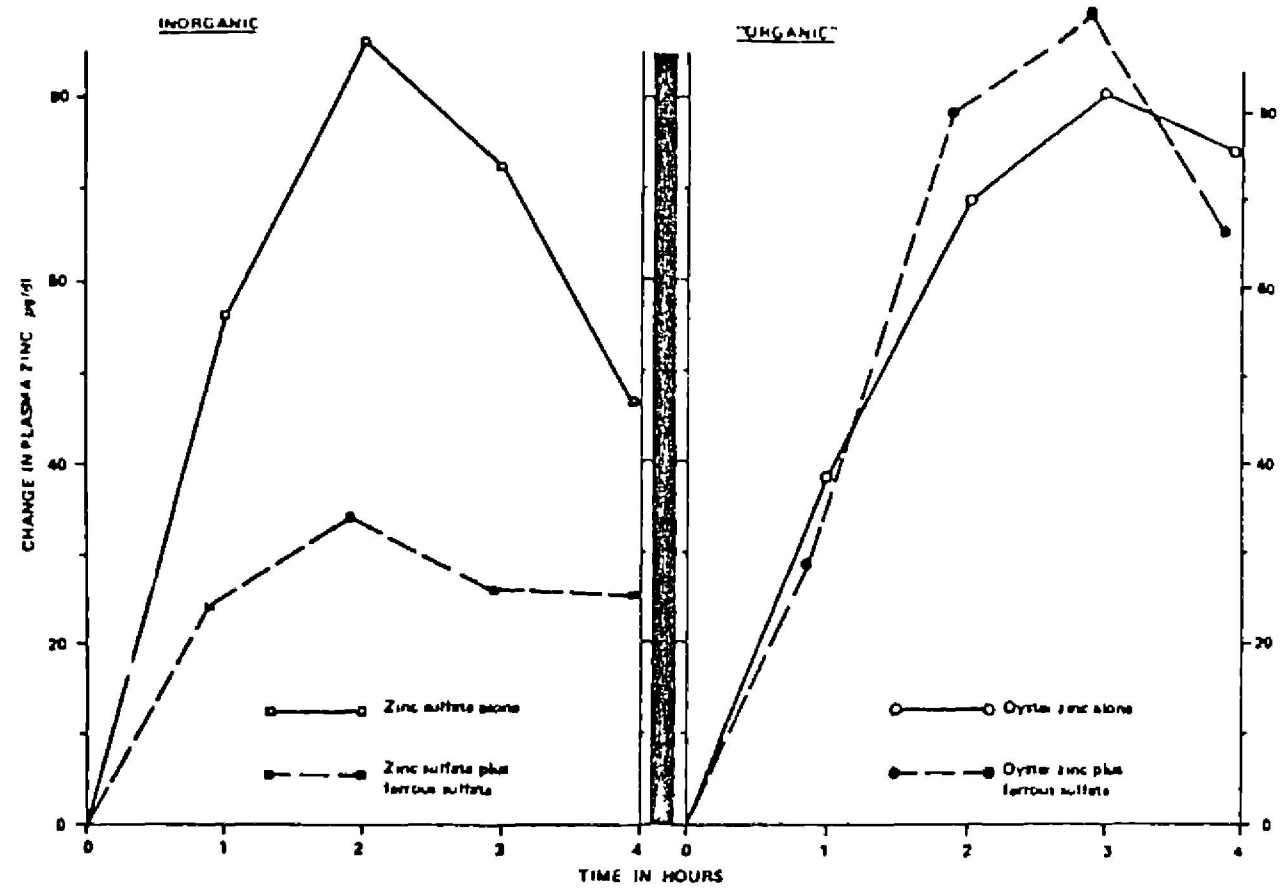

FIG. 4. *Two sets of experiments in which zinc was administered alone, or with iron in a 2-to-1 iron-to-zinc ratio. In the curves to the left, the source of zinc was zinc sulfate, and the iron was ferrous sulfate; the iron reduced the area under the curve by more than 50 percent. In the curves to the right, the zinc was administered as raw oysters and the iron as ferrous sulfate; no difference in these curves was observed.*

would not be prudent no matter how brief the exposure or how attenuated the dosage, stable isotopes offer a viable research alternative. One could even consider labeling the zinc in maternal milk by feeding stable zinc to a nursing mother and determining its absorption in her infant without risk to either party.

Studies in experimental animals over the past 25 years have implicated various feeds based on soy-protein as inhibitors of zinc availability. Consumption of an increasing number of analogs of meat and dairy products based on vegetable protein—specifically isolated soybean protein—has raised concern about a possible detrimental effect on zinc nutriture in the populations of industrialized nations. Clinical studies under way in our laboratories at the Massachusetts Institute of Technology and at the Clinical Center of the Institute of Nutrition of Central America and Panama in Guatemala should help to clarify the comparative bioavailability of zinc from soy-based baby formulas and texturized meat-extenders and from the standard foods they are replacing.

Finally, a number of fundamental physiological questions remain to be addressed. For instance, which, if any, among the proposed candidates for the intrinsic ZBL really function at a physiologically important level in the human intestine? Moreover, in the obviously copious turnover and reabsorption of zinc in the enteropancreatic circulation, is endogenous zinc from pancreatic secretions more or less completely absorbed than dietary zinc? To what degrees and under what circumstances does the homeostatic regulation of zinc absorption by the intestine have a nutritionally important significance in man?

The data at hand at the present time amply demonstrate that the biological availability of zinc is a major determinant factor in the maintenance of normal zinc nutriture. The application of our knowledge of zinc bioavailability in evaluating consumption patterns or in providing therapeutic diets may pay substantial dividends now, even before all of the biological issues have been resolved.

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