In a remarkably short time, our perception of Zn has progressed from that of a rather obscure essential trace mineral of doubtful significance for human health to that of a micronutrient of exceptional biologic and public health importance. This is most evident in relation to both prenatal and postnatal development. This article 1) provides an overview of our rapidly evolving recognition of the ubiquitous biological roles of Zn; 2) reviews what we have learned, particularly in the last 10–15 y, about the global public health importance of Zn deficiency as a major cause of morbidity and mortality in young children; 3) critically reviews potential strategies for preventing and treating zinc deficiency; and 4) considers food-based strategies for preventing Zn deficiency with special attention to the use of meat, including organ meat, starting at the earliest stage of introduction of complementary feeding.

### Biology of Zn

Zn is second only to iron among those elements for which a human nutritional requirement has been established. The adult human body contains ~2 g (1). In contrast to iron, Zn is located relatively evenly throughout the body, especially as a component of thousands of Zn metalloproteins or Zn-binding proteins and also of nucleic acids. Therefore, Zn is not as readily detectable as iron and presents a persistent challenge of detecting and diagnosing Zn deficiency by Zn concentrations in plasma or serum and other tissues. Of outstanding biologic value is the ability of Zn to participate in strong but readily exchangeable ligand binding (2), interacting with a wide range of organic ligands that incorporate Zn into myriad biologic systems.

The biologic role of Zn is now recognized in structure and function of proteins, including enzymes, transcription factors, hormonal receptor sites, and biologic membranes. Zn has numerous central roles in DNA and RNA metabolism (3), and it is involved in signal transduction, gene expression, and apoptosis. Zn metalloenzymes and zinc-dependent enzymes have been identified and are involved in nucleic acid metabolism and cellular proliferation, differentiation, and growth (4).

A major advance in our understanding of the biology of Zn was the identification of proteins that contain a Zn finger motif (5), a recurring pattern of amino acids with conserved residues of cysteine and histidine at the base to which Zn binds in a tetrahedral arrangement. Hundreds of Zn finger motifs have been and continue to be identified. Over 3% of all identified human genes contain Zn finger domains (6). Thus, Zn plays a broad role in gene expression.

Zn plays a regulatory role in apoptosis (7), with cytotoxic functions that suppress major pathways leading to apoptosis and also directly influences apoptotic regulators triggered by a decline in intracellular Zn. Zn can modulate cellular signal recognition, second-messenger metabolism, and...
protein kinase and protein phosphatase activities. In the brain, Zn is sequestered in the presynaptic vesicles of Zn-containing neurons and is released into the cleft and then recycled into the presynaptic terminal (8). Zn plays a role in modulation of brain excitability. Vesicular-rich regions such as the hippocampus are responsive to dietary Zn deprivation. Finally, the Zn atom per se, in contrast to iron and copper, has no oxidant properties, and it exists virtually entirely in the divalent state, which has simplified its incorporation into biologic systems and its safe transport, both extra and intracellularly.

The public health significance of zinc deficiency
Human Zn deficiency was first hypothesized with considerable supportive evidence in the early 1960s (9). This hypothesis was be related to adolescent nutritional dwarfism in Egypt and Iran (10) and was also noted at younger ages (11). These important observations were not adequately confirmed with randomized controlled trials of zinc supplementation and remain areas for future research. A virtual void in pursuing the public health implications of Zn deficiency in the developing world ensued for almost a quarter of a century, during which the focus was on dealing with the identification of acute severe Zn deficiency states, secondary Zn deficiency in various disease states, vulnerability of the low-birth-weight infant to Zn deficiency, and occurrence of nutritional growth-limiting Zn deficiency in otherwise healthy infants (12) and young children (13).

More recently, the public health importance of Zn deficiency was documented by a number of rigorous randomized, double-blinded, placebo-controlled trials (RCTs)3 of Zn supplementation in young children in the developing world (14). A prominent and early effect of restricting dietary Zn models is impairment of weight gain and linear growth velocity (15). Initially, Zn supplementation RCTs focused on growth velocity in young children. A comprehensive meta-analysis of results of 33 studies provided convincing evidence of a significant increase in linear growth, with a weighted average effect size of 0.350; this was deemed of global practical importance (16,17). Growth faltering starts at ~6 mo of age in less-developed countries (LDC) with rapid progression (18) and coincides with a critical time in the dietary supply of Zn, labeled as a “problem” nutrient in complementary feeding by WHO (19).

By 1990, it was apparent that persistent diarrhea, a major cause of morbidity and mortality, did not respond to antibiotics. Its association with stunting pointed to malnutrition as a possible contributing factor. Moreover, macronutrient deficiencies did not readily explain the association. Interest and focus turned to micronutrient deficiencies. The importance of Zn for immune system integrity (20), the known losses of Zn in diarrheal fluids (21), and pilot data on the association between Zn deficiency and diarrhea (22) all resulted in Zn becoming a micronutrient of major interest. Major RCTs of Zn supplementation for prevention and treatment of both acute and persistent diarrhea in several LDC ensued. Pooled analyses of the results provided convincing evidence for a beneficial effect of Zn supplements in prevention (~15% reduction in incidence) (23) and treatment (14) of both acute and persistent diarrhea. Less expected was the effectiveness of Zn supplements in preventing pneumonia, a major cause of early childhood mortality in the developing world (23). Thus, a reduction of mortality (24) as well as morbidity was found to be attributable to Zn supple-

3 Abbreviations used: IOM, Institute of Medicine; LDC, less-developed countries; RCT, randomized, double-blinded, placebo-controlled trials; RDA, recommended dietary allowances.

Food sources of zinc for infants
The feasibility and potential of a local nonfortified food-based approach for preventing onset of Zn deficiency in infancy are challenging. An infant of 6–8 mo is in the critical transition period of infancy, with a calculated Zn concentration in human milk is <1 mg/L (28), and the intake of Zn from breast milk by the exclusively breast-fed 7-mo infant is only 0.5–0.6 mg regardless of the mother’s Zn status (28,29).

Complementary foods in LDC are typically limited almost entirely to plant foods. Zn concentrations in even the most favorable plant foods are inadequate to meet requirements (30). This problem is compounded by unfavorable bioavailability attributable to the inhibitory effect of phytate (31). Plant foods with the most favorable Zn concentrations, notably grains and legumes, also have the highest phytate concentrations. Challenging research is now being directed to biofortification of grains with Zn (32) and to lowering phytate (33). Micronutrient fortification of food staples provides a partial solution to achieving adequate Zn in plant foods. However, these fortified foods will not reach all older infants/toddlers, especially the millions of rural poor (34). Similar constraints are encountered with the availability of sprinkles (35), yet to be shown efficacious in preventing or managing Zn absorption/deficiency. There remains a compelling current and long-term need for locally produced nonfortified complementary foods providing adequate Zn. Animal-source foods, especially meats, including organ meats, not only contain the highest concentrations of Zn (17) but provide zinc in a bioavailable form.

Potential contribution of meat to achieving adequate Zn intake at 7 mo of age
**Dietary Zn.** Zinc has been classified by WHO as a “problem” nutrient in complementary feeding (19), i.e., a micronutrient for which requirements cannot be met without supplementation or fortification of complementary foods given to breast-fed infants starting at ~6 mo of age. This conclusion was based on subtracting the estimated average intake of energy and Zn from breast milk at age 7–11 mo from estimated dietary requirements for this age as established by WHO/FAO (36) or the Food and Nutrition Board, Institute of Medicine (IOM) (37), and then calculating the ratio of Zn deficit (mg) per 100 kcal. A ratio of 0.7 mg Zn/100 kcal was determined to meet the recommended dietary allowances (RDA) of 3 mg/d for Zn of the IOM (37). This ratio was then compared with those calculated for nonfortified complementary feedings in 5 countries for which adequate data were available. None of the latter, including 4 other LDC and the United States, met the estimated ratio needed (19).

One ounce of beef provides ~1.6 mg Zn and 80 kcal, for a Zn (mg):energy (kcal) ratio of 2.0. With a further 0.5–0.06 mg/d Zn from breast milk, the breast-fed infant aged 7 mo would require...
only 0.9 mg Zn from other sources to meet the RDA (37). Because 270 kcal were also calculated to be required, other foods would require a Zn:energy ratio of only 0.3 to achieve the RDA for Zn for infants aged 6–11 mo (37). Indeed, the RDA for Zn could be met even with a less-demanding energy goal. These calculations indicate that Zn is not necessarily a “problem” nutrient when meat (± liver) is one of the first and regular complementary foods.

**Quantity of Zn absorbed.** The potential contribution of meat to achieving adequate Zn absorption at age 7 mo can also be assessed by estimating the quantity of Zn absorbed and its contribution to meeting physiologic requirements. Measurements have been made of Zn absorption from single test meals of beef by infants aged 7 mo (38). Also shown was that fractional absorption of Zn over an entire day was lower if administered with breast milk.

The physiologic Zn requirement for infants aged 6–11 mo is 0.84 mg Zn/d, as recently agreed by 2 committees (17,37). Plotting the physiologic requirement on the saturation response model in Figure 1 gives an estimation of dietary Zn requirement necessary to meet this physiologic requirement of 2.2 mg Zn/d. It is noted that this estimation is close to the IOM estimated average requirement for Zn for this age group of 2.5 mg Zn/d (37). It is this figure that is targeted in calculating the potential contribution of meat/liver to meet dietary requirements and match these to physiologic requirements.

Figure 1 depicts average Zn intake and absorption from breast milk at age 7 mo for infants in whom breast milk continues to be the principal or only source of liquid nutrients at that age. These quantities of Zn are far short of estimated physiologic and dietary requirements. The additional small increment in Zn intake and absorption provided by cereal containing phytate is shown in the control group for the Colorado study. Absorption of Zn from this food should be estimated from a different saturation-response curve that is specific for the phytate content (39). However, the phytate is so low in milled rice cereal, and the estimated quantity of Zn absorbed from the rice cereal is already so low (Fig. 1), that any adjustment for phytate would be virtually undetectable. Even with the additional increment from ad libitum nonmeat complementary foods, both Zn intake and absorption were only approximately half the estimated dietary and physiologic Zn requirements, respectively.

In contrast, the average increment in both Zn ingestion and Zn absorption from beef in gravy at 7 mo of age in the above Colorado study (40) was sufficient to meet estimated dietary and physiologic Zn requirements in the beef group. Other noncereal foods contributed an additional modest increment. By 9 mo, the Zn intake from complementary meat foods increased by a further 0.5 mg Zn/d. These data highlight the special value of meat in any food-based approach to providing adequate Zn starting in midinfancy and also for providing iron and several vitamins. There is a strong argument for giving priority, whenever possible, to inclusion of meat in increasing the diversity of complementary foods.

**Acceptance of meat in midinfancy**

The acceptability of meat as a first and regular complementary food starting in midinfancy (7 mo) to achieve dietary, especially physiologic requirements for Zn, is a key issue.

In a RCT of beef puree vs. infant cereal as the first complementary food for exclusively or predominantly breastfed Colorado infants between 5 and 7 mo of age, acceptance scores for the beef were the same as those for infant cereal (40). During the study, the cereal group could not eat beef and vice versa. Other complementary foods were permitted ad libitum. By 7 mo of age, beef group infants were consuming, on average, 2 oz/d of “beef and beef gravy” second food (Gerber Products Co., Fremont, MI), which provided 1.6 mg Zn/d, similar to the average Zn content of just 1 oz of cooked beef (41).

Minced liver was readily accepted by infants in the Western Highlands of Guatemala (Fig. 2). Zinc concentration in liver is even higher than that in beef, and it is easily ground or mashed. The high vitamin A content may limit liver intake to no more than 2–3 feeds per week.

**Practical considerations**

Significant barriers exist to providing meat as a first complementary food in many circumstances. Sociocultural, economic, and household factors may be important barriers (42). Mother’s lack of awareness of the importance of animal-source foods in the diet for infants and young children influences consumption. Some populations have genuine population-wide religious reasons for not consuming meat. Preferential food allocation patterns for adult male household members limit the amount of meat available for infants, young children, and women in many developing countries. There are some regions/populations where/for which environmental/agricultural conditions limit successful household production (43,44), and populations cannot afford to purchase meats. Limited availability and accessibility of animal products, especially flesh foods, are common in many developing country populations. Lack of knowledge about the hygienic care, preparation, and preservation of flesh foods is also limiting. Preparation in an appropriate form for consumption in infancy (i.e., puree, not spicy) can be problematic.
Barriers can be overcome using professionals skilled in behavior change. There is ready acceptance of meat/liver as the first complementary food for infants with appropriate interventions. Cultural norms are often being renegotiated. Moreover, in some populations, failure to provide affordable meats/liver results from “common practice” rather than any more complex cultural reason. This is true also in industrialized countries. The recent Colorado study (40) has demonstrated ready acceptance of beef as the first complementary food without adverse effect. In many communities, household production of meat, especially small animals, i.e., rodents, birds, or fish, is possible. There are many recent encouraging experiences with enhancing local food production, often initiated by international agencies or nongovernmental organizations (45–47). However daunting, local food-based solutions to achieving adequate complementary feeding remain the only option for many poor populations. Even partial success is eminently worthwhile in populations with varying degrees of access to affordable fortified products.

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