Zinc Nutrition from Discovery to Global Health Impact1–3

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The 2012 ASN History Symposium “Zinc Nutrition from Discovery to Global Health Impact” celebrated Ananda S. Prasad’s recognition of primary zinc deficiency in humans (1). His success resulted from his curiosity, observational skills, critical thinking, and knowledge of history. At the time, human zinc deficiency was thought very unlikely. Reviewers discussed aspects of the rich history of zinc as a nutrient. The respective reviews will be published in this journal.

Harold H. Sandstead introduced the symposium and events associated with Prasad’s findings and their confirmation. The index case, a male Iranian farmer aged 21 y, had, beginning in childhood, frequently consumed clay. His diet based on whole-meal, wheat flat bread sometimes included vegetables and egg but almost never red meat. He was pale, stunted, and physically and sexually undeveloped. His nails had spoon-like deformities and his abdomen hepatosplenomegaly. He was severely anemic and intolerant of exercise. Ten similar patients were also studied. Iron deficiency, the primary cause of anemia, was considered an unlikely cause of stunting and hypogonadism. The effects of zinc deficiency in other species supported Prasad’s hypothesis that the individuals were zinc deficient. He later confirmed his hypothesis through studies in similarly afflicted Egyptian farmers (2–4).

Wolfgang Maret discussed the chemistry of zinc in biology. Though zinc was reported essential for Aspergillus niger in 1869, chemical mechanisms involving zinc were elusive until 1939, when carbonic anhydrase was reported to require zinc. Later, covalent binding of zinc with S, N, and O donor groups of cysteine, histidine, and glutamate and aspartic acids became evident. In 2006 it was reported that the human genome encodes >3000 zinc-binding proteins, including >1000 enzymes and 1000 nuclear transcription factors. Other research discovered intracellular zinc-containing vesicles that release ionic zinc for several purposes. For example, axon terminals of glutaminergic neurons in the Ammon’s Horn region of the hippocampus are rich in zinc-containing vesicles. They release ionic zinc into the neural cleft during neurotransmission. The zinc then binds with NMDA receptors on dendrites, where it modulates excitation. More recently it was found that picogram amounts of zinc released from vesicles in the endoplasmic reticulum of cells serve as second messengers. Thus, understanding the many fundamental roles of zinc for life continues to be revealed.

Forest Nielsen summarized the history of zinc in agriculture. In 1914, the essentiality of zinc maize was reported. By 1926, it became evident that all higher plants need zinc. By 1972, zinc deficiency was considered the most common plant micronutrient deficiency in the US. The constant presence of zinc in egg yolk and human and cow milk was interpreted in 1919 as evidence in favor of its essentiality for farm animals and humans. Technical problems delayed an animal model of the 1930s. In 1955, it was reported that swine confined to concrete pens and fed diets rich in phytate and calcium became stunted, had severe dermatitis and diarrhea, and died if not treated with zinc. The findings were soon confirmed in chicks. By 1972, zinc deficiency was reported as the most common plant micronutrient deficiency in the United States and now it is estimated that nearly one-half of the soils in the world are low in available zinc. The consequences include low production of grain and other products if soil is not amended with zinc. Thus, zinc deficiency is endemic among herbivores in many parts of the world. It is now known the zinc supplements in Guyana, Greece, southern and western Australia, and Idaho improved production. Prevention includes zinc-containing salt licks for grazing animals and zinc-adequate grain concentrates for confined animals.

Rosalind S. Gibson discussed dietary zinc intakes as an indicator of zinc status of populations. Interference of phytate with zinc absorption was suspected to be causal, based on effects in swine and chicks, when primary zinc deficiency was first discovered in Iranian and Egyptian farmers and...
characterized. In the US, the 1976 Total Diet Study by the U. S. FDA reported a mean daily zinc intake in adults of 13.3 mg. It was notable that this intake of zinc was similar to that consumed by the deficient individuals noted above. By 1980, the list of foods analyzed for zinc increased to at least 300. The use of zinc isotopic tracers provided data on the effects of various diet constituents on zinc retention. Phytate:zinc molar ratios provided estimates of absorbable dietary zinc and their relationship with zinc biomarkers in persons from low income countries (LIC). In the 1990s, an increased understanding of factors governing zinc absorption led to the refinement of zinc requirements and algorithms for the estimation of dietary zinc bioavailability. Subsequently, the estimated average (daily) requirement for zinc was used as the criterion for determining the prevalence of zinc deficiency in populations. A current interpretation suggests that risk of zinc deficiency should be considered of public health concern when the prevalence of inadequate intakes is >25%. Recent data indicates that zinc bioavailability from high-phytate, whole-day diets is substantially lower than previous studies suggested. Thus, interpretation of zinc EAR in LIC might warrant a reexamination.

K. Michael Hambidge discussed the clinical aspects of zinc deficiency using acrodermatitis enteropathica as an example of the most severe zinc deficiency. Illness is caused by mutations in the extracellular portion of the trans-membrane zinc transporter, Zip4. Normally, Zip4 upregulates the absorption zinc. When this does not occur, zinc deficiency is soon evident. Progressive morbidity, including acrodermatitis, growth arrest, infections, etc., and death occur. When patients are adequate in other micronutrients, restoration of zinc status rapidly restores homeostasis. However, severe zinc deficiency is unusual. The most common patients can be diagnostically difficult, because they show limited physical evidence but are metabolically and functionally impaired. Adverse effects can include low immunity, increased susceptibility to inflammation, poor healing, suppressed neuropsychological functions, etc. The effects of low zinc status on immunity are recognized as a major cause of morbidity from diarrhea and pneumonia in infants of LIC. High dietary consumption of phytate substantially increases the risk of zinc deficiency. Published estimates of prevalence range from 20 to 50%. Understanding the role of human zinc nutrition and deficiency, whether it be in the individual or population, is a journey in progress.

Ananda S. Prasad discussed his recent work and suggested areas for future research. His work on zinc essentiality for cell immunity, resistance to oxidative stress, and antiinflammation has revealed underlying mechanisms. Thus, concurrent zinc deficiency complicates morbidity from chronic diseases by suppressing immunity, increasing oxidative stress, and increasing the generation of inflammatory cytokines. The role of chronically low zinc status in the pathogenesis of atherosclerosis, certain cancers, certain neurological disorders, and autoimmune diseases is incompletely understood. Dr. Prasad suggested future research on chronic diseases might include comparison treatment trials designed to evaluate the efficacy of zinc.

**Literature Cited**