

# This Week's Citation Classic®

Sandstead H H, Prasad A S, Schuler A R, Farid Z, Miale A, Bassilly S & Darby W J. Human zinc deficiency, endocrine manifestations and response to treatment. *Amer. J. Clin. Nutr.* 20:422-42, 1967.

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Endocrinologic characteristics of 40 Egyptian village boys, ages 12-20 years with stunting delayed puberty and iron deficiency, were studied. Plasma zinc (mean  $\pm$  SD) was  $64.7 \pm 12.4$  mg% ( $n=102 \pm 13$ ). Responses to intravenous ACTH and metyrapone were generally low. Pituitary gonadotropin levels were low. Oral glucose tolerance tests were consistent with delayed absorption in many. In the zinc-treated group, growth occurred in spite of the fact that the subjects were iron deficient. [The *SCI*<sup>®</sup> indicates that this paper has been cited in over 215 publications.]

## Zinc Deficiency: Growth Stunting and Hypogonadism

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I arrived at the US Naval Medical Research Unit Number 3, Cairo, Egypt, in 1961, for a two-year assignment as a Public Health Service officer. My assignment was to work with a nutrition research team directed by William J. Darby of Vanderbilt University (Program Project, Interdepartmental Committee on Nutrition, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health). Ananda S. Prasad had arrived several weeks earlier. Ananda, with his colleagues James A. Halsted and M. Nadimi, had reported the association of geophagia, iron deficiency, dwarfism, hypogonadism, and hepatosplenomegaly in adolescent boys from villages near Shiraz, Iran.<sup>1</sup> Ananda shared his impressions with Professor Darby, and it was decided that we would study the zinc nutriture of severely growth-retarded adolescent boys from villages near Cairo. As a junior member of the team, I was given the responsibility of measuring indices of the endocrine status and the growth responses of the boys. Other reports by the Vanderbilt group described the major clinical characteristics of the syndrome and the kinetics of <sup>65</sup>Zn in the subjects and their excretions of zinc in urine and sweat. The syndrome was also described in boys from an oasis far from Cairo where hookworm and schistosomiasis did not occur. We also documented zinc deficiency in infants with severe protein energy malnutrition and children with thalassemia.

Looking back, it appears to me that the seminal observations of Prasad, Halsted, and Nadimi and the subsequent research of the Vanderbilt group in Egypt and the group led by Halsted, Reinhold, and Ronaghy in Iran provided the impetus for a remarkable growth in knowledge of the importance of not only zinc, but other trace elements for human physiology. Prior to this work, only iron, iodine, fluorine, and cobalt were considered to be of practical importance as far as human health was concerned. Deficiencies of zinc and other trace elements were known to occur in farm animals but were considered quite unlikely to be important for human health. This attitude changed rapidly following the reports from Egypt and Iran. By 1971 the importance of trace minerals for human health was sufficiently accepted, and the World Health Organization (WHO) appointed a committee chaired by Darby and Eric Underwood to review knowledge of the trace element requirements of humans. Proceedings of that meeting were published. The chapter on zinc was based in part on data generated from the studies in Cairo and Iran and on factorial calculations of requirements I had prepared for a Federation of American Societies for Experimental Biology-American Institute of Nutrition Symposium.<sup>2</sup> Since then, research on trace elements and their relationship to disease has progressed rapidly, and the WHO and the Food and Agriculture Organization have convened another expert committee to review current knowledge.

Several factors will make such advances possible. Perhaps the most important is improved technology for analysis and for tracer studies. The development of techniques for maintaining trace mineral-free environments has been critical for studies in experimental animals. Research in experimental and farm animals has clearly demonstrated the importance of interactions among trace elements and between trace elements and other substances in diets. Clinical investigations of these interactions will better define human dietary requirements for trace minerals and factors that influence bioavailability.

From my personal viewpoint, this era of trace element research has been highly exciting and entertaining. Advances are coming so fast that the applied scientist is hard-pressed to keep up. As far as zinc is concerned, it is now apparent that it is essential for expression of the genome, that zinc nutriture modulates neutralization of active oxygen species, and that it is perhaps a factor in mutagenesis and heritable mutations. Factors that influence the bioavailability of zinc and human dietary requirements for zinc are becoming better understood. This knowledge will be vital for the prevention of human zinc deficiency. A recent review of the role of zinc in human biology edited by Colin F. Mills of the Rowett Research Institute is recommended to those who are interested in nutrition and factors that influence zinc's bioavailability.<sup>3</sup>

1. Prasad A S, Halsted J A & Nadimi M. Syndrome of iron deficiency, anemia, hepatosplenomegaly, hypogonadism, dwarfism, and geophagia. *Amer. J. Med.* 31:532-46, 1961. (Cited 295 times.)
2. Sandstead H H. Zinc nutrition in the United States. *Amer. J. Clin. Nutr.* 26:1251-60, 1973. (Cited 250 times.)
3. Mills C F, ed. *Zinc in human biology*. Berlin, FRG: Springer-Verlag, 1988. 388 p.

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