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Prasad A S, Miale A, Farid Z, Sandstead H H, Schulert A R & Darby W J. Biochemical studies on dwarfism, hypogonadism, and anemia. *Arch. Intern. Med.* 111:407-28, 1963.
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Biochemical and nutritional characteristics of 17 patients who exhibited the syndromes of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism, and geophagia were studied in Egypt. These patients suffered from dietary deficiencies of both iron and zinc. Later studies showed that growth retardation and male hypogonadism were related to zinc deficiency. [The *SCI*® indicates that this paper has been cited in more than 250 publications.]

Deficiencies of Iron and Zinc

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After completing my residency in medicine under C.J. Watson at the University of Minnesota, I went to Shiraz, Iran. There, I described a syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism, and geophagia in southern Iran.[1] It was not clear, however, if this syndrome was unique to Iran.

In 1961, working under William J. Darby, Vanderbilt University Medical School, I moved to the US Naval Medical Research Unit Number 3 in Cairo, Egypt. We discovered that the syndrome noted in Iran was also common in the delta villages of Egypt—with some differences. The Iranian subjects were more anemic, the Egyptian subjects did not give a history of geophagia, and, whereas the Egyptian subjects had both schistosomiasis and hookworm infections, the Iranian patients suffered neither.

Although the anemia in both countries was related to iron deficiency, the extreme growth retardation and hypogonadism in males could not be accounted for on this basis. The male subjects, who had chronological ages of 16 to 23 years, looked like 8- to 10-year-old boys.

In 1910, I.I. Lemann[2] described similar clinical manifestations in subjects who suffered from hookworm infection in the southern US. He related the growth retardation to hookworm disease. In Egypt and China, a common belief among physicians was that growth retardation was due to schistosomiasis infection. Older physicians in Lebanon told me personally that they related dwarfism to malaria parasites. In Iran, physicians related the growth retardation to hypopituitarism but were unable to reconcile with the high incidence of this syndrome. A report from Turkey[3] suggested that iron deficiency in pregnancy led to lack of proper growth and development.

We established that iron deficiency alone accounted for the anemia. Liver function tests and liver biopsy revealed no evidence of liver cirrhosis. In all cases, the subjects ate only cereal proteins high in phosphates and phytates, which adversely affected the availability of iron and zinc. Although geophagia was clearly common in Iran, this was not the case in other countries. We encountered no other deficiencies (proteins, calories, vitamins, or minerals).

Our later studies in Egypt established that the dwarfs were also zinc deficient.[4] Supplementation with zinc corrected the growth and gonadal abnormalities but had no effect on anemia;[5] iron supplementation corrected the anemia, but it had no effect on growth and gonadal development. Our current estimate is that both iron and zinc deficiencies are prevalent throughout the developing world, and we speculate that growth retardation observed in these populations may be related to a deficiency of zinc.

Since the original description of this syndrome and demonstration that, indeed, zinc is essential for humans, tremendous progress has been made in the understanding of the biochemical functions of zinc.[6] Today it is estimated that 300 enzymes require zinc for their activities, and as many as 500 nucleoproteins may require zinc for their binding to DNA molecules. These discoveries have greatly impacted my career, and I have continued my active involvement in the search for the understanding of the various roles of zinc in human health.

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 315 times.) [See also: **Prasad A S.** A diet of zinc or clay. Citation Classic. *Current Contents/Life Sciences* 34(28):11, 15 July 1991.]
2. **Lemann I I.** A study of the type of infantilism in hookworm disease. *Arch. Intern. Med.* 6:139-46, 1910.
3. **Reimann F.** Growth anomalies and malformations in iron-deficient states. *Proceedings of the 5th Kongr. Eur. Gesellschaft Haematol.* Freiburg, FRG: Keller, 1955. p. 546-50.
4. **Prasad A S, Miale A, Farid Z, Sandstead H H & Schulert A R.** Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypogonadism. *J. Lab. Clin. Med.* 61:537-49, 1963. (Cited 325 times.) [See also: **Prasad A S.** Zinc deficiency in humans. Citation Classic. *Current Contents/Clinical Medicine* 17(38):14, 18 September 1989; and *Current Contents/Life Sciences* 32(38):14, 18 September 1989.]
5. **Sandstead H H, Prasad A S, Schulert 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. (Cited 225 times.) [See also: **Prasad A S.** Zinc deficiency: growth stunting and hypogonadism. Citation Classic. *Current Contents/Clinical Medicine* 17(16):16, 17 April 1989; and *Current Contents/Life Sciences* 32(16):17, 17 April 1989.]
6. **Prasad A S.** Discovery of human zinc deficiency and studies in an experimental human model. *Amer. J. Clin. Nutr.* 53:403-12, 1991.

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