BIOCHEMISTRY OF THE ELEMENTS
Series Editor: Earl Frieden

Biochemistry of Zinc

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To my family

Preface

During the past three decades, remarkable advances have taken place in the field of zinc metabolism. Prior to 1963, its deficiency in humans was unknown. Today, it is recognized that a nutritional deficiency of zinc is common throughout the world, including the United States.

The growth retardation in children and adolescents commonly seen in developing countries is likely related to a nutritional deficiency of zinc. In the same areas variable immune deficiency disorders are common. Because of the important role of zinc in immunity, such disorders may also be a result of nutritional deficiency of zinc.

Diagnostic criteria for a mild or marginal deficiency of zinc, which appears to be common in the developed countries, have yet to be established, although considerable progress has been made recently in characterizing this state of zinc deficiency clinically, biochemically, and immunologically.

Besides nutritional deficiency of zinc, conditioned deficiency of this element caused by several disease states is probably common. This knowledge is likely to improve clinical management of various chronic illnesses. The discovery that a fatal genetic disorder, acrodermatitis enteropathica, is a genetically induced zinc deficiency syndrome has resulted in a complete cure of this condition, and indeed many lives have been saved by simple therapeutic oral administration of zinc. Mandatory use of supplemental zinc in fluids used for total parenteral nutrition has substantially reduced serious complications that were being induced by a severe deficiency of zinc prior to its parenteral administration. Recent recognition that therapeutic zinc is an effective means of decreasing copper burden in humans has now led to an effective nontoxic therapy for Wilson's disease. These are just a few examples of recent clinical advances in the field of zinc metabolism.

Very impressive advances have also taken place in our understanding of the basic aspects of zinc metabolism during the past three decades. Thirty years ago we knew of only three enzymes that require zinc for their activities; today we know of approximately 200 such enzymes. Recent increases in our knowledge of zinc-finger proteins and their roles in genetic expression of var-

ious growth factors and steroid receptors are truly exciting. This area is advancing rapidly, as evidenced by the number of papers being published. Zinc has been shown to control mRNA of metallothionein, a low-molecular-weight protein highly rich in cysteine. Rapid advances have taken place in the understanding of the structure and function of this protein. Its role in ameliorating heavy metal toxicity, in absorption of copper and zinc, and perhaps as a donor of zinc to apoenzymes has been documented only recently. Inasmuch as this protein is an excellent scavenger of hydroxyl ions, and zinc induces the synthesis of this protein, zinc may play an important role in free radical reactions.

Although the need for zinc for lymphocyte proliferation has been known since 1970, only recently has it been discovered that even a mild deficiency of zinc in humans may result in anergy, decreased production of IL-2 and IL-1, decreased natural killer cell activity, and decreased levels of active thymulin peptide. These observations may lead to correction of zinc-related immune disorders in the future and may have an impact on the clinical management of various patients.

The present volume does not discuss zinc toxicity except in its interaction with copper. In human studies, with the exception of copper deficiency, I have not been impressed with the toxic effects of zinc provided the level of zinc administration has been less than 50 mg/day orally.

I have included a chapter on technique, which deals with the assay of zinc in plasma and blood cells by atomic absorption spectrophotometry. My goal here is to encourage clinical laboratories to establish proper techniques for assessment of zinc status in humans.

An attempt has been made to cover important biochemical areas related to zinc and its functions. This field has grown so rapidly that it is impossible to do it justice in a monograph such as this. Nonetheless, this is a first attempt to bring together all the basic knowledge and relate it to the clinical effects of zinc deficiency in a readable fashion.

I sincerely hope that this book will provide stimulus for new research. The book should prove to be useful to students of nutrition and biochemistry, and to physicians who are likely to encounter many zinc-related problems in their practice.

I most sincerely thank Mary Yuhas, Mary Ann Gavura, Barbara Foulke, Sally Bates, and Tom Panczyszyn for their invaluable help in the preparation of this volume.

Ananda S. Prasad

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Historical Aspects of Zinc 1

1.1 Zinc Deficiency in Microorganisms, Plants, and Animals

Raulin (1869) was the first to show that zinc was essential for the growth of *Aspergillus niger.* This was confirmed forty years later by Bertrand and Javillier (1911). In 1926, its essentiality for higher forms of plant life was established (Sommer and Lipman, 1926) (see Figs. 1-1 and 1-2).

Todd *et al.* (1934) established for the first time that zinc was needed for the growth of the rat. Earlier attempts by Bertrand and Benson (1922), McHargue (1926), and Hubbel and Mendel (1927) to demonstrate the essentiality of zinc in animals were unsuccessful, because the purified diets employed were deficient in other essential elements besides zinc.

Tucker and Salmon (1955) reported that zinc could cure and prevent the disease called parakeratosis in swine (see Figs. 1-3 and 1-4). O'Dell and his colleagues (1958) showed that zinc was essential for the growth of birds.

Zinc deficiency in suckling mice that were deprived of colostrum was reported by Nishimura (1953). The manifestations consisted of retarded growth and ossification, alopecia, thickening and hyperkeratinization of the epidermis, clubbed digits, deformed nails, and moderate congestion of certain visceral organs. Miller and Miller (1960) produced an experimental deficiency of zinc in calves. The main features were growth failure, testicular atrophy, and hyperkeratosis. Deficiency of zinc in the diet of breeding hens was shown to result in (1) lowered hatchability, (2) gross embryonic anomalies characterized by impaired skeletal development, and (3) varying degrees of weakness in chicks that hatched (Blamberg *et al.,* 1960).

By feeding dogs a diet low in zinc and high in calcium, a deficiency was produced whose clinical features included retardation of growth, emaciation, emesis, conjunctivitis, keratitis, general debility, and skin lesions on the abdomen and extremities (Robertson and Burns, 1963). In young Japanese quails, zinc deficiency was induced by feeding a low-zinc purified diet containing soy protein, which resulted in slow growth, abnormal feathering, la-

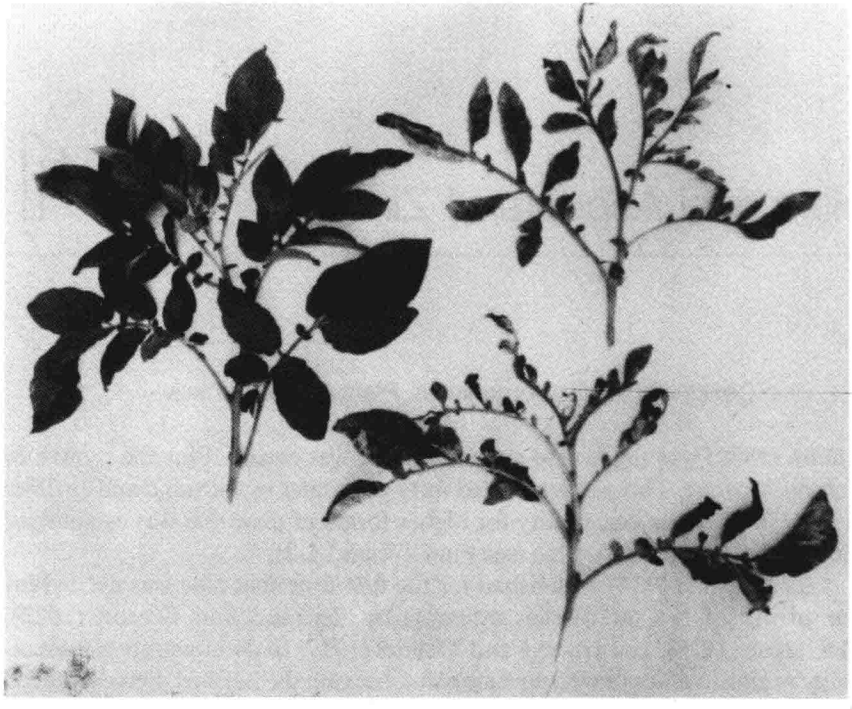

Figure 1-1. "Fern leaf" of Russet Burbank potatoes caused by a deficiency of zinc is shown on the right. [Reprinted with permission from Viets, F. G., 1966. Zinc deficiency in the soil–plant system, in *Zinc Metabolism* (A. S. Prasad, ed.), Thomas, Springfield, Ill. p. 90.]

bored respiration, incoordinate gait, and low content of zinc in the liver and tibias (Fox and Harrison, 1964).

1.2 Zinc Deficiency in Humans

Although the essentiality of zinc for animals has been recognized since 1934, its ubiquity made it seem unlikely that alterations in zinc metabolism could lead to significant problems in human nutrition or clinical medicine. This attitude has now changed.

In the fall of 1958, while I was visiting Iran, Dr. J. A. Halsted brought to my attention a 21-year-old male at Saadi Hospital, Shiraz, who looked like a 10-year-old boy. Besides severe growth retardation, his clinical features included hypogonadism, severe anemia, hepatosplenomegaly, rough and dry

Figure 1-2. Zinc-deficient onions on the right. [Reprinted with permission from Viets, F. G., 1966. Zinc deficiency in the soil–plant system, in *Zinc Metabolism* (A. S. Prasad, ed.), Thomas, Springfield, Ill., p. 90.]

skin, mental lethargy, and geophagia (Prasad *et al.*, 1961). The patient ate only bread made of unleavened wheat flour and the intake of animal protein was negligible. He ate one pound of clay per day. It became apparent to us later that the habit of geophagia (clay eating) was fairly prevalent in the villages around Shiraz. Our studies showed that the anemia was caused by a deficiency of iron but there was no evidence of blood loss. Hypopituitarism as an explanation of growth retardation was ruled out, inasmuch as ten additional similar cases were brought to my service for further studies within a very short period of time (see Fig. 1-5). We considered the following probable factors responsible for anemia in these cases: (1) The total amount of available iron in the diet was insufficient; (2) excessive sweating in a hot climate probably caused greater iron loss from the skin than would occur in a temperate climate; and (3) geophagia may have further decreased iron availability as was observed later by Minnich *et al.* (1968). The anemia was completely corrected by administration of oral zinc in every case.

Lemann (1910) had described similar clinical features in patients with hookworm infection but he did not relate these to a nutritional deficiency. Similar cases from Turkey were described by Reimann

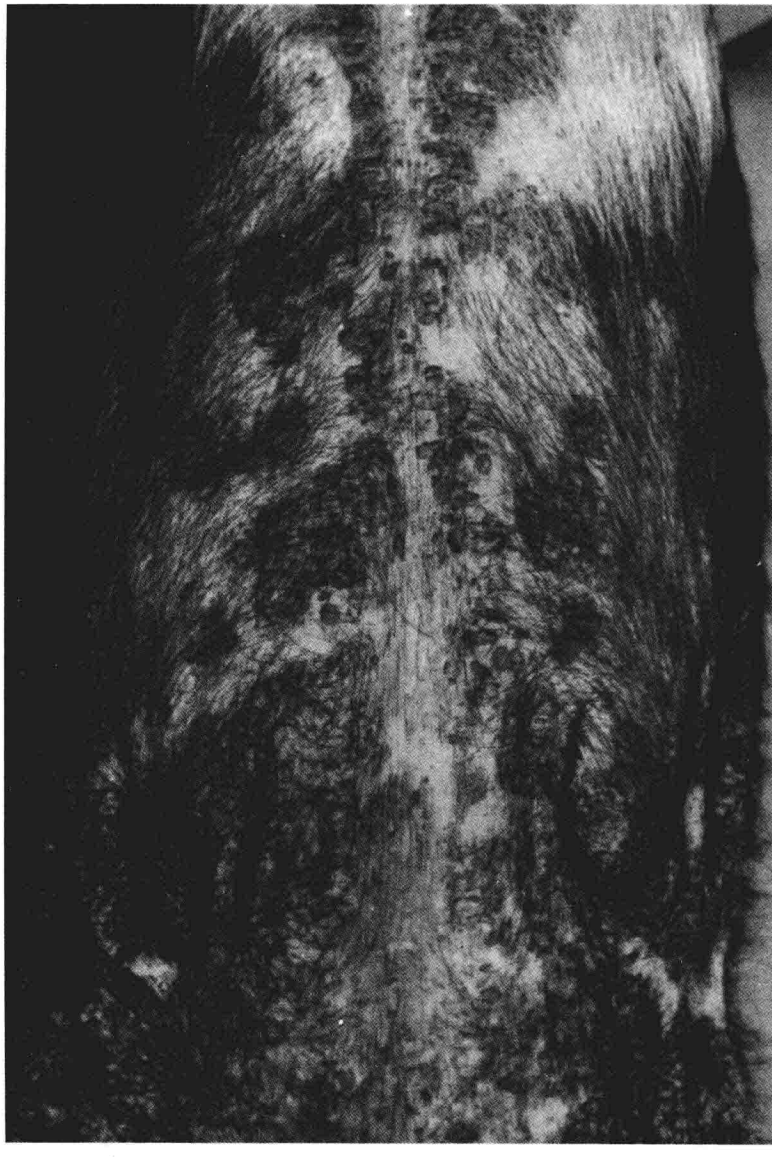

Figure 1-3. A view of the abdomen of a parakeratotic pig. [Reprinted with permission from Leucke, R. W., 1966. The role of zinc in animal nutrition, in *Zinc Metabolism* (A. S. Prasad, ed.), Thomas, Springfield, Ill., p. 202.]