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A Biography

Early Life
I was born in Buxar, a small town in the state of Bihar, India. At age four, I suffered from typhoid fever, a serious infectious disease for which no antibiotics were available at that time. I remained in bed for nearly three months. My parents gave up hope for my life but somehow, I survived. One year later, we were hit by a very strong earthquake. The whole neighborhood was destroyed. Many lives were lost. By God’s grace, my mother and four sisters survived. Although our house was completely destroyed, a small terrace was left intact in one corner of the house, where my mother and sisters remained standing. I was in the front yard, playing with my two nephews. The ground split and water rushed out from underground. We were totally shocked. A few minutes later, I heard my mother’s voice who instructed us not to come near the building because the bricks were still falling. My father, who was a police officer under the British government, was out of town on duty. There was a complete disruption of all modes of transportation and he walked on foot for seven days to reach home. Having heard about the terrible devastation due to the earthquake in our town, he was afraid that none of his family would be found alive when he reached home.

My oldest brother, who was twenty years older than me in age, worked as a Magistrate under the British Government in another town nearly fifty miles away. He rushed to our town to see us by train. Unfortunately, there was another after-shock and the train was derailed. He suffered severe injuries, fractured his arm, but thank God, he lived to see us in our tent after the earthquake.

Later my brother decided to take me to his town, Arrah, where I could enter a school. Our state has three major rivers and as luck would have it, during monsoon season, after my arrival in Arrah, we had a terrible flood. The whole town was submerged under six feet of water. One of our family friend had a three story house and we all stayed there for several days until the flood water had subsided.

I was admitted to Arrah Zila School in fourth grade at the age of six. I was completely unprepared and I did very poorly in all subjects during the first term. My father was planning to take me out from the school and prepare me for this level at home before re-entering this class, but I decided to continue. I studied hard and by the end of the year, I was the top student in the class and I continued this position throughout my high school. I graduated from high school as the top student at age fourteen.

My brother was transferred from Arrah. I then moved to my eldest sister’s house who also lived in Arrah and continued my schooling. Her husband was a practicing attorney.
I had a very sad experience of my life at age eleven when my father expired. He was only fifty-six. He was very sick with kidney failure. I was not informed about his sickness until his end was near. I was taken to the hospital in Patna, the capitol of Bihar, where he was admitted. He was semi-conscious. He did not recognize me. He only remembered my oldest brother. I watched him fade away to death before my eyes. I remember very vividly even today, the rainy night when my father expired. The entire family was there. All of us were crying. I felt that my world had ended. I lost my security blanket and my future looked grim. My oldest brother, who was a great human being, assured me that he will take care of me as my father. Although my brother had four of his own children, he truly treated me as his son. He educated me, guided me and sent me to USA for higher medical studies. I was the youngest in my family. My mother, four older sisters and two older brothers were very kind, affectionate and very caring, and this helped me to grow up in an ideal family environment.

After graduation from high school, I joined Patna Science College, Patna University. I was top student in chemistry and received B.Sc degree with honors in mathematics.

During my college years, I witnessed India’s independence movement led by Mahatma Gandhi. His non-violent peaceful movement for independence had great influence on young students. We were impressed by Gandhi’s philosophy and ideologies. I was very fortunate to be closely associated with one great political figure, Mr. Rajendra Prasad, who became the first President of independent India. He was my neighbor and a distant relative. He was a true follower of Mahatama Gandhi, completely selfless and greatly devoted to India’s independence.

Medical School and higher training in USA
My family assumed that I would compete for the Indian Civil Service under the British government, but this hope was dashed when, soon after gaining independence, the Indian government abolished this service. I was consequently urged to study medicine, and I entered the Patna Medical College in Bihar, graduating there in 1951 with high distinction in physiology. I found physiology fascinating and wanted to learn more. Education in India was oriented towards England. However, following independence, I learned about the opportunities for studies in the USA from one of my professors who had departed from the usual custom and had traveled in the USA as well as in England. Fortunately for me, an American program for 40 highly selected Indian physicians was announced. I was one of those selected. In 1952 I went to St. Paul’s Hospital, Dallas, Texas, for residency training in pathology, accompanied by my wife, who sought further training in obstetrics and gynecology. Contrary to the route taken by my classmates, I decided not to seek Membership in the Royal College of Physicians (MRCP), England, and looked for additional training in the USA, much to the disappointment of my family, who perhaps never forgave me; this eventually meant permanent departure from India.

I was fortunate to be accepted by Dr. C.J. Watson, a well known outstanding Professor of Medicine, for training in internal medicine at the University of Minnesota Medical School, and this undoubtedly was the single most important event in my career. Under Dr. Watson, a superb teacher, an excellent biochemist, and an effective investigator, I spent the next five
years working with Dr. Edmund Flink, a member of Dr. Watson’s department. I was trained at Minnesota to be a clinical scientist. My research subjects were calcium and magnesium metabolism. Thus began a lifelong interest in the metabolism of various elements, including zinc. Hematology was learned under Dr. Dorothy Sundberg, the exceptionally able morphologist who had been trained by Professor Hal Downey. I also profited from Watson’s own interest in heme synthesis.

As a Resident I studied and published a case history of an unusual patient who had hepatosplenomegaly and lymphadenopathy as well as hemolytic anemia and thrombocytopenia. This turned out to be a case of acquired agammaglobulinemia and was one of the earliest observations in the area of immunodeficiency disorders. Another exciting patient was an extremely obese man who had polycythemia. I and Max H. Weil concluded that the polycythemia was secondary to obesity and decreased ventilation, actually anticipating the well-known description of the Pickwickian syndrome by Burwell.

As an exchange visitor I could not remain in the USA. Moreover, I was also interested in returning to India. My interest was in an academic post in India, a position I failed to achieve because of my lack of British training. Fortunately, Dr. Hobart A. Reimann, who had preceded Dr. Watson as Chief of Medicine in Minnnesota, was now appointed as Chief of Medicine at the Nemazee Hospital of Pahlevi University in Shiraz, Iran, and he invited me to go to Iran. He was a personal friend of the Shah of Iran. In spite of my initial reluctance, I accepted Dr. Reimann’s offer to join him in Shiraz, where I discovered zinc deficiency.

Discovery of Human Zinc Deficiency
Raulin in 1869 showed for the first time that zinc was essential for the growth of Aspergillus niger (Raulin J. Chemical studies on vegetation. Ann Sci Nat 11 (in French), 93-99, 1869). In 1933 Todd et al. reported that zinc was essential for the growth of the rats. In animals the manifestations of zinc deficiency included growth failure, loss of hair, thickening and hyperkeratinization of the epidermis, and testicular atrophy (Todd WR, Elvehjem CA, Hart EB. Zinc in the nutrition of the rat. Am J Physiol, 107:146-156, 1933). Although the essentiality of zinc for animals was established, its ubiquity made it seem improbable that zinc deficiency in humans could lead to significant problems in clinical medicine.

I arrived in Shiraz, Iran, in June 1958. In Shiraz, I met Dr. James, A. Halsted, who was a Fulbright Professor at Pahlevi University and was primarily involved with Saadi hospital. Dr. Halsted was married to Anna Roosevelt, the daughter of President Franklin D. Roosevelt. In the fall of 1958, I was invited by Dr. Halsted to discuss a patient with anemia at the medical center grand rounds at the Saadi Hospital. The case was presented to me by the chief resident, Dr. M. Nadimi, a graduate of the Shiraz Medical School.

The patient was a 21-y-old male, who looked like a 10-y-old boy. In addition to severe growth retardation and anemia he had hypogonadism, hepatosplenomegaly, rough and dry skin, mental lethargy, and geophagia. The patient ate only bread from wheat flour and intake of
animal protein was negligible. He consumed nearly 0.5 kg of clay daily. Later we discovered that the habit of geophagia (clay eating) was fairly common in the villages around Shiraz. Further studies documented the existence of iron-deficiency anemia in our patient but, there was no evidence of blood loss. Inasmuch as 10 additional similar cases were brought to the hospital under my care within a short period of time, hypopituitarism as an explanation for growth retardation and hypogonadism was ruled out.

The anemia of the subjects promptly responded to oral administration of iron. The probable factors responsible for anemia in these patients were insufficient availability of iron in the diet, excessive sweating probably causing greater iron loss from the skin than would occur in a temperate climate and geophagia further decreasing iron absorption.

It was difficult to explain all of the clinical features solely by tissue iron deficiency inasmuch as growth retardation and testicular atrophy are not seen in iron-deficient experimental animals. The possibility that zinc deficiency may have been present was considered. As noted earlier, zinc deficiency was known to produce retardation of growth and testicular atrophy in animals. Because heavy metals may form insoluble complexes with phosphate, we speculated that some factors responsible for decreased availability of iron in these patients with geophagia may also have decreased the availability of zinc. O’Dell and Savage (1960) had observed that phytate (inositol hexaphosphate), which is present in cereal grains, markedly impaired the absorption of zinc. (O’Dell BL, Savage JE. Effect of phytic acid on zinc bioavailability. Proc Soc Exp Biol Med, 103:304-306, 1960).

We published a clinical description of the Iranian cases as a syndrome and speculated that zinc deficiency may account for growth retardation and male hypogonadism in these subjects (Prasad AS, Halsted JA, Nadimi M. Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism, and geophagia. Am J Med, 31:532-546, 1961). I left Iran in January 1961 and joined the department of Biochemistry and Medicine of Vanderbilt University under Dr. William J. Darby. Although Dr. Darby wanted me to study porphyrin metabolism in Pellagra in Egypt, I shared with him my speculation that zinc deficiency in the Middle East was prevalent and was responsible for widespread growth retardation. He approved my plans to investigate zinc metabolism in growth-retarded subjects. I then moved to U.S. Naval Medical Research unit No.3 (NAMRU-3), in Egypt. My team consisted of Harold Sandstead, MD, and A. Schulert, PhD, both from Vanderbilt University, A. Miale Jr. MD from US Naval Medical Research Unit No.3 (NAMRU-3) and Z. Farid, MD, a local physician, also from NAMRU-3.

In Egypt subjects similar to the growth-retarded Iranian subjects were encountered. The clinical features were remarkably similar except that the Iranian subjects had more pronounced hepatosplenomegaly, a history of geophagia, and no hookworm infection and the Egyptian subjects had both schistosomiasis and hookworm infestations but no history of geophagia.

We carried out a detailed investigation of the Egyptian cases at NAMRU-3 in Cairo. The dietary history of the Egyptian subjects was similar to that of the Iranians. The consumption of animal
protein was negligible. Their diet consisted mainly of bread and beans (Vicia fava). These subjects were shown to have zinc deficiency. The evidences were decreased zinc concentrations in plasma, red cells, and hair and studies with zinc-65 revealed that the plasma zinc turnover was greater, the 24-h exchangeable pool was smaller, and the excretion of zinc-65 in stool and urine was less in the subjects than in the control subjects (Prasad, A.S., Miale A, Farid Z, Sandstead HH., Schulert A., Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypogonadism. J Lab Clin Med, 61:537-549, 1963).

Hypozincemia in humans in the absence of advanced cirrhosis of the liver had not been described before. Liver-function tests and biopsy revealed no evidence of cirrhosis in these subjects. Furthermore, in contrast to cirrhosis patients who excrete abnormally high quantities of zinc in urine, our patients excreted less zinc in urine than did control subjects. Other chronic debilitating diseases that might affect the serum zinc concentrations were also ruled out.

It was a common belief among clinicians in Iran that severe growth retardation and sexual hypofunction, as noted above, were the results of visceral leishmaniasis and geophagia. In our studies no evidence of visceral leishmaniasis was found. The role of geophagia was not entirely clear; however, it was suspected that the excess amount of phosphate in the clay may have prevented absorption of both dietary iron and zinc. The predominantly wheat diet in the Middle East, now known to contain high quantities of phytate and fiber, most probably reduced the availability of zinc. In Egypt, the cause of dwarfism was commonly considered to be schistosomiasis. Chinese investigators had also implicated schistosomiasis as a causative factor for growth retardation.

Our studies in the Middle East only included males. Female subjects refused to participate in our studies. Later studies from Iran by Halsted et al. (Halsted JA, Ronaghy HA, Abadi P, Haghshenass M, Amirhakimi GH, Barakat RM, Reinhold JG. Zinc deficiency in man: The Shiraz Experiment. Am J Med, 53:277-284, 1972), demonstrated that zinc deficiency in females manifesting growth retardation was prevalent.

Studies in Egypt showed that the rate of growth was greater in patients who received supplemental zinc as compared with those receiving iron instead or those receiving only an adequate animal-protein diet (Sandstead HH, Prasad AS, Schulert AR, Farid Z, Miale A, Bassily S, Darby WJ. Human zinc deficiency, endocrine manifestations and response to treatment. Am J Clin Nutr, 20:422-442, 1967). Pubic hair appeared in all subjects within 7–12 wk after zinc supplementation. Genitalia increased to normal size and secondary sexual characteristics developed within 12–24 weeks in patients who received zinc. In contrast, no such changes were observed in a comparable length of time in the iron-supplemented group or in the group on an animal-protein diet. Thus, the growth retardation and gonadal hypofunction in these subjects were related to zinc deficiency. The anaemia was due to iron deficiency and responded to oral iron treatment.
It is now evident that nutritional as well as conditioned deficiency of zinc may complicate many disease states in human subjects. In 1968 MacMahon et al. (MacMahon RA, Parker ML, McKinnon M. Zinc treatment in malabsorption. Med J Aust, 2:210-212, 1968), observed, for the first time, zinc deficiency in a patient with steatorrhea. Several other examples of zinc deficiency in patients with malabsorption have now been recorded. In 1972 a number of Denver children from middle-class families, were reported to show symptomatic nutritional zinc deficiency (Hambidge KM, Hambidge C, Jacobs M, Brown JD. Low levels of zinc in hair, anorexia, poor growth and hypogeusia in children. Ped Res, 6:868-874, 1972). Growth retardation, poor appetite, and impaired taste acuity were related to zinc deficiency in those children and all the symptoms were corrected with zinc supplementation.

In 1973, Barnes and Moynahan (Barnes PM, Moynahan EJ. Zinc deficiency in acrodermatitis enteropathica. Proc R Soc Med, 66:327-329, 1973), studied a 2-y-old girl with severe acrodermatitis enteropathica who was being treated with diiodohydroxyquinoline and a lactose-deficient synthetic diet. The clinical response to this therapy was not satisfactory and the physicians sought to identify contributing factors. The concentration of zinc in the patient’s serum was profoundly decreased; therefore, they administered oral zinc sulfate. The skin lesions and gastrointestinal symptoms cleared completely and the patient was discharged from the hospital. When zinc was inadvertently omitted from the child’s regimen, she suffered a relapse; however, she promptly responded to oral zinc. In their initial reports the authors attributed zinc deficiency in this patient to the synthetic diet. It soon became clear that zinc might be fundamental to the pathogenesis of this rare inherited disorder and that the clinical improvement reflected improvement in zinc status. This original observation was quickly confirmed in other patients throughout the world. The underlying pathogenesis of the zinc deficiency in these patients is due to malabsorption of zinc due to a mutation in ZIP4, a zinc transporter (Wang K, Zhou B, Kuo YM, Zemansky J, Gitschier J. A novel member of a zinc transporter family is defective in acrodermatitis enteropathica. Am J Hum Genet, 71:66-73, 2002).

In 1974 a landmark decision to establish recommended dietary allowances (RDAs) for humans for zinc was made by the Food and Nutrition Board of the National Research Council of the USA National Academy of Sciences.

In 1978 zinc was included in total parenteral nutrition fluids which resulted in saving many lives.

Factors contributing to my successful research career
It’s hard to define what led me to succeed in my research pursuit. I had no plan or desire to go to Iran initially but very unusual circumstances took me there. I sometimes wonder what would have happened if I never went to Iran. What would have been the state of knowledge concerning the role of zinc in human health? Perhaps my prepared mind, hard work and confidence in my hypothesis, led me to discover the essentiality of zinc from human health. Although I faced many controversies, I remained persistent and this has resulted in my recognition.
I have published over 300 papers and fifteen books. I was founding editor of two journals, American Journal of Hematology and Journal of Trace Elements in Experimental Medicine. I have continued my research activities throughout my academic career. I have received much recognition for my contributions. These include AMA Goldberger Award, American College of Physicians Award for outstanding work in science as related to Medicine, Medal of Honor from Mayor of Lyon, France, First Raulin Award for pioneering research in zinc from International Society for Trace Elements Research in Humans (ISTERH), Robert H. Herman Award from American Society of Clinical Nutrition, Mastership from the American College of Physicians, inducted in the Heritage Hall of Fame, International Institute Foundation, Detroit, Michigan and Asian Academy Hall of Distinction Award, Washington, DC.

Most importantly I received the 2010 Prince Mahidol Award from Bangkok. This was truly a great honor, and the function in Bangkok was very memorable and elegant, which I enjoyed immensely.

Prince Mahidol was truly a visionary. To paraphrase the prince, “To gain knowledge is not enough, to apply the knowledge to solve the problems of public health should be the goal.” This should serve as a goal post for all clinical scientists. Prince Mahidol’s contribution to the Mahidol University, Medical Center and public health in Bangkok is indeed legendary.

I had many collaborators and co-workers who contributed greatly to the advancement of this field. I acknowledge their contributions gratefully.

Impact of my discovery that zinc is essential for human health
When I first described human zinc deficiency from Iran and Egypt nearly fifty years ago, it was not clear if this problem was prevalent worldwide. Today it is estimated that zinc deficiency affects nearly two billion subjects, mainly in the developing world. This is because most of these populations subsist on cereal proteins which contain high amounts of organic phosphate compound, phytate which complexes zinc and makes it unavailable for absorption. One would also expect to see a spectrum of zinc deficiency, ranging from severe cases to marginally deficient examples, in any given population.

The health consequences of this deficiency are severe. I never saw a zinc deficient dwarf live beyond the age of twenty-five in Iran and Egypt. Extreme growth retardation, hypogonadism, severe immune deficiency disorders, and cognitive impairment are major consequences of zinc deficiency in humans. I am hoping that one day, this deficiency is wiped out completely.

The mortality rate in infants and children due to acute diarrhea used to be 85%. Ever since zinc has been supplemented in the perfusion fluid, the mortality has declined to 15 per cent. Millions of children are now living because of this treatment. (Sazawal S, Black R, Bhan MK, Bhandarin N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. N Eng J Med, 33: 839-844, 1995).
Wilson's disease is a genetic disorder in which copper excretion is defective and this leads to excessive accumulation of copper in the liver, pancreas, kidneys and brain. It's truly a most disabling disorder with a limited life span. Ever since zinc has been developed as a therapeutic tool for Wilson's disease, the patients are doing remarkably well and living a better quality of life. (Brewer GJ, Hill GM, Prasad AS, Cossack ZT, Rabbani P. Oral zinc therapy for Wilson's disease. Ann Int Med, 99:314-320, 1983). Zinc has been now approved by FDA as a therapeutic agent for management of Wilson's disease.

Recent Cochrane review shows hat zinc is an effective agent for treatment of common cold which affects millions of subjects every year throughout the world. Proper zinc lozenges (zinc acetate or zinc gulanonate) in optimal doses, taken every three to four hours and once started within 24 hours of the onset of common cold, reduces the duration and severity by fifty percent. In view of the fact that no other treatment has been found effective, this is truly an important therapeutic modality for common cold.

Age related macular degeneration leads to blindness in several millions of elderly subjects worldwide. In studies conducted by NIH Eye Institute has shown that zinc supplementation alone reduces the incidence of blindness by 27% in subjects with dry type of macular degeneration, thus saving sight in millions of elderly subjects. (AREDS Report No.8. A randomized placebo controlled clinical trial of high-dose supplemented with vitamins C and E, beta carotene, for age-related macular degeneration and vision loss. Arch Ophthal, 119:1417-1436, 2001).

Our studies have shown that nearly 30% of the well to do elderly subjects and 60% of the subjects with sickle cell disease are zinc deficient. In both of these conditions, zinc supplementation reduces the incidence of infection by 65%. This observation is very important and one should use zinc supplementation for prevention of infections in these conditions.

My return to USA
I received an immigration visa to come to the USA in 1963 and was offered the position of Chief of Hematology at Wayne State University. I remained in Detroit as Director of the Division of Hematology until 1984. In Detroit I made additional observations of unique interest; for example, a 17-year old black female with excessive uterine bleeding whose fibrinogen level was found to be normal or zero, depending on whether the ammonium sulfate technique or the thrombin assay methods was being used. With the collaboration of E.F. Mammen and the Blombacks of Stockholm, fibrinogen Detroit was described (Blomback M, Blomback B, Mammen EF, Prasad AS. Fibrinogen Detroit - A molecular defect in the N-terminal disulfide knot of human fibrinogen? Nature, 218:134-137, 1968). In the same year I discovered an unusual family of patients who had sex-linked sideroblastic anemia and this provided an opportunity to show that in that family the sideroblastic gene was linked to the G6PD gene on the X chromosome (Prasad AS, Tranchida L, Konno ET, Berman L, Albert S, Sing CF, Brewer GJ. Hereditary sideroblastic anemia and glucose-6-phosphate dehydrogenase deficiency in a negro
family. *J Clin Invest, 47:1415-1424, 1968*). I also found zinc deficiency in adult sickle cell anemia subjects and has provided evidence that the growth retardation, hypogonadism, and other manifestations, including impaired healing of leg ulcers in males with sickle cell anemia, may be related to zinc deficiency. My current research is concerned with the relationship of zinc to cell-mediated immunity.

**My Family**

My eldest brother, who became, my guardian after my father’s death died in 1955, at the age of 47 while I was still in training at the University of Minnesota Medical School. He had severe hypertension and at that time, in India the management of hypertension was very poor. I had very much hoped that I could bring him to USA for proper treatment, but unfortunately it did not happen. I was very shocked and regretted greatly that I could not see him after I left India. During the past two decades all my sisters, my mother, and my other brother, have all expired and now for me, my home town is a sad place. I went there recently and found the whole city very lonesome. Only memories are now left.

I married my close friend and classmate in medical school, Aryabala, who practiced obstetrics and gynecology in Michigan. She accompanied me to Iran and Egypt, remained exceedingly supportive of my research career and raised four lovely children. Three of my children, Rita, Sheila and Ashok became physicians and are practicing medicine within forty miles of my residence. My youngest daughter, Audrey, who was born in Iran, did her MBA and is currently employed in marketing and sales in Michigan. I have nine grandchildren and four great grandchildren. Our family is closely knit and we truly care for each other. I feel that I am truly blessed.