

1969

Zinc : a survey of recent research in zinc metabolism as it relates to the human body

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ZINC
A SURVEY OF RECENT RESEARCH IN ZINC METABOLISM
AS IT RELATES TO THE HUMAN BODY

A Thesis
Presented to the Faculty of
The University of Nebraska College of Medicine

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Medicine

by
Dale Leverne Mock

June 1969

PREFACE

Recently, the author had the opportunity to become involved in research in the micronutrient metabolism of plants. The interrelations of micronutrient metabolism in regard to plant nutrition, growth, and reproduction, was a focal point. Although other micronutrients were studied, the primary emphasis was placed upon zinc and its role in plant growth.

It has been successfully shown that zinc does play a very essential role in plant growth. Since many plant and animal enzyme systems are essentially the same, the importance of zinc in the human body in relation to growth, function, and the welfare of man, presents unanswered questions to me. Among the questions one must examine in studying any micronutrient, are; (1) is the element found in the body, if so, where, and in what proportions? (2) How is the element involved in humans and just what is its importance in human metabolic systems? (3) What role is played in human disease? (4) How can the element be used to alleviate human suffering?

I propose to answer these questions with respect to zinc in an effort to reach some conclusions on the importance of this element in human metabolism.

I wish to acknowledge and thank Doctor Paul Hodgson for his help and assistance in the preparation of this thesis,

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CHAPTER I

INTRODUCTION

Since man began, he has been vitally interested in the effects of the substances which make up his environment upon his body. Initially, man was interested in food or potential food substances. He was concerned whether excesses or deficiencies of these substances had any influence on his health. Later, man became aware that disease processes could be related to a variety of identifiable causes in which nutrition played a role, and during the past forty to fifty years, intense study of the mechanisms of diseases was focused on the effects of excesses or deficiencies of the basic substances, such as mineral elements, vitamins, hormones, and enzymes.

The research in zinc metabolism has roughly paralleled man's quest.

The presence of zinc in muscles and liver was first discovered in 1877 (79). However, the need for zinc in human nutrition was actually demonstrated only recently.

Early indications for a biologic function for zinc may be given by citation of the early literature on the effects of zinc; Raulin, in 1869, proved zinc was a necessary nutrient to *Aspergillus niger* (80). Mendel and Bradley in 1906, produced evidence that zinc was an essential constituent of the respiratory pigment of the snail, *Sycotypus*,

analogous to the hemocyanins (56). In 1919, Delezene reported a very high concentration of zinc in snake venom, and then showed it to be in a stable combination with the intensity of the venom action directly proportional to the concentration of zinc (13). Conclusive evidence of the essential nature of zinc in the rat diet was produced in 1934 by Todd and co-workers (94).

Although conclusive evidence of the zinc requirement for man and higher animals was not proven until recently, Keilin and Mann in 1939, showed zinc to be present in the prosthetic group of the enzyme carbonic anhydrase and suggested that zinc must be required in nutrition because of the wide presence of carbonic anhydrase in many animal species (41).

CHAPTER II

ZINC IN BODY TISSUES, ORGANS, AND FLUIDS

1. Whole Body

The total body zinc stores in the average adult human ranges between 1.2 and 3 grams. This is about one half the biologic store of iron, 10-15 times the store of copper and 40 times that of iodine. The amount of zinc supplied by an average daily diet is approximately 10-15 mg, but, as is the case of most orally ingested substances, the fraction actually absorbed from the intestinal tract is influenced by

numerous physiologic mechanisms (96, 48, 103).

Apparently, there is little, if any, evidence of appreciable storage of zinc by the fetus, as occurs with iron and copper. The concentration of zinc in the human fetus changes little throughout fetal life and the liver and spleen together always contain approximately the same proportion (roughly one-quarter) of the total zinc (111).

Newborn and very young mammals seem to be more variable than adults in zinc content and tend to contain somewhat lower, or similar, concentrations of the element at birth and maturity. However, the values given in the literature for some newborn animals (cat, guinea pig, rabbit) may be abnormally high if one considers the increased amount of hair on these animals in comparison to mouse, rat, and human values. Hair and fur contain much higher concentrations of zinc than almost all other body tissues.

The normal range of zinc concentration in the human body has been estimated by various authors to be 15 to 60 parts per million and depending upon the method used, various values may be quoted for zinc content of a particular tissue. The ubiquitous nature of zinc, in addition to the relatively insensitive methods of zinc analysis up until recent years, has probably accounted for this great variation of quantitative values seen for zinc levels in tissues.

2. Tissue Distribution

Isotopic zinc studies seem to demonstrate a continual tissue deposition and turnover of zinc which varies greatly with different tissues. Zinc-65 injected into the body has the highest turnover rate in pancreas, liver, kidney, pituitary, and adrenal glands. Muscle, erythrocytes, brain and testes exchange zinc less rapidly, whereas zinc is deposited in the skeleton and teeth relatively slowly, but, found for relatively long periods of time. Zinc deposited in hair remains there until the hair is shed.

In terms of absolute concentrations, the pigmented tissues of the eyes, hair, and bones, carry far higher concentrations of zinc than other body tissues and organs.

3. Eye Structures

Tissues of the eye contain large quantities of zinc. Vallee has compiled a large number of references into a survey of species of vertebrates which not only indicates marked species differences, but marked differences in the zinc distribution within a single eye (103). The zinc content of lens and aqueous humor is not remarkable in any species, but the choroid and retina seem to have outstandingly high values in most cases. Probably the highest known concentration of zinc in living matter occurs in the melanin-pigmented tissues of the eyes of some fresh water fishes (trout, perch). The pigment-protein complex constituted 41.6% of the dry weight of the perch choroid, accounting

for 74% of the zinc content of this tissue (6).

As stated above, species and individual differences exist, but the various eye tissues can be placed in the same order in respect to zinc concentrations in each of the species examined. This order, in descending concentrations of zinc, is as follows: Iris, choroid (plus pigment epithelium), retina (minus pigment epithelium), lens, aqueous and vitreous humor, sclera, cornea, and optic nerve (6).

The eyes of colored and albino rabbits were studied. Zinc levels of 127 and 466 P.P.M. were found in the iris and choroid respectively of the colored animals, compared with 54 and 86 P.P.M. for these tissues in the albinos (7).

The intravenous injection of 100 mg/kg body wt. of dithiophenylcarbazon, a chelating agent of zinc and other metals, causes blindness in dogs within 24 hours due to inactivation of zinc by chelation (103).

It has been shown by Bliss that horse liver alcohol dehydrogenase can catalyze the redox interconversion of Vitamin A¹ alcohol and aldehyde. In the retina, this reaction is catalyzed by retene reductase which indicates this may be identical or similar to alcohol dehydrogenase (5).

4. Epidermal Structures

Although zinc has been found in essentially all body tissues, a preponderant 15 to 20% of the total body stores is concentrated within the skin and its accessory structures(31).

What useful function zinc plays in these tissues is yet unknown, but as will be pointed out later, a definite function of zinc in the skin is indicated beyond that of being a simple storage reservoir.

In beriberi, a thiamine deficiency, a marked decrease of zinc concentrations was observed in blood, hair, skin, and nails (87). Eggleton also produced evidence of an interesting correspondance between beriberi and the zinc concentration of human epidermal structures. Subnormal levels of zinc were found in hair, nails, and skin of beriberi patients. Essentially, the values for zinc are one half of the levels found in corresponding epidermal structures (16).

Various authors working with zinc deficient dietary regimens have described skin hair, hoof or mucosal disorders in a variety of animals. Barney described a parakeratosis of tongue mucosa to be a unique pathologic lesion in zinc deficient monkeys (2). Mills in Britain has described, among other manifestations of zinc deficiency response, alopecia, hyperkeratosis of skin in areas of hair loss, a coarsening of wool or hair growth and alterations in the structural growth of hooves in both lambs and calves (59).

Day, also Prasad, working with rats, has described similar hair coat and skin changes in that animal after being placed on a zinc deficient diet (12, 78). A similar type of skin lesion termed "parakeratosis" has been studied, described

and treated in pigs in the U.S. since the 1940's (43, 95).

Reinhold and his fellow workers studying nutrition in rural Iranian villages in the vicinity of Shiraz, a region in which the occurrence of zinc deficiency has been previously observed in humans, found zinc concentrations of hair to be significantly lower in village residents than in similar control population in Shiraz. Village diets consisted predominately of flat bread prepared from locally grown cereal grains, other locally grown vegetables and relatively little animal protein. City diets were diversified and abundant in fruits, vegetables, and meats brought from widely spread localities (81).

Although zinc concentrations in hair was significantly lower than those in controls, values for copper and nitrogen concentrations did not differ between the two groups. This fact that there was no difference in copper and nitrogen values indicates that the dietary insufficiency probably is not due to decreased protein intake (81).

Lowest zinc concentrations occurred in the village women. Results of these studies provide evidence that concentrations of zinc in human tissues may be depleted, presumably as a result of limited intake (or decreased absorption) and possibly increased losses of zinc (as in child-bearing and lactating women) (81).

5. Male Genital Tissues

Zinc concentrations of 1-2 mg per gram of dried human semen have been reported (54). Differences between sperm and semen plasma were considered insignificant, though a variable but significant percentage of seminal plasma zinc was found to be dialyzable.

Zinc concentration in the human testes have been variably reported, but are, in general, higher than zinc levels in other body tissues, except eye tissues.

Saito et al recently studied the zinc content of sperm taken from various levels of the dog reproductive tract, similar to the previous study done in rats by Birnbaum (83, 4). "Preprostatic" zinc levels were determined on sperm taken from dog testes, epididymis and vas. Canine ejaculate sperm zinc and canine seminal zinc determinations were also made. The latter value was 1.75 mgZn/g dry wt. The results (see table 1.) indicate essentially no zinc uptake by sperm in the dog until after the sperm have passed through the prostate and have been bathed by the prostatic secretions. This would seem to indicate that a function of the dog prostate is to contribute zinc to the spermatozoa. In the rat, the zinc content (0.86 mg Zn/g dry wt.) of spermatozoa from the epididymis is similar to the level reported (by Birnbaum) in ejaculated spermatozoa (0.89 mg Zn/g dry wt.) the determinations being made by similar and comparable methods. However, Birnbaum, in his study, found that zinc uptake by rat spermatozoa began

TABLE 1.
 COMPARISON ZINC LEVELS IN SPERM OF TWO SPECIES
 TAKEN FROM VARIOUS LEVELS OF THE
 REPRODUCTIVE TRACT

Investigator	Testes	Epididymis	Vas	Ejaculations
Saito (dog)	0.15	0.16	0.18	1.04
Birnbaum (rat)	0.39	1.18	1.29	0.89

NOTE: All values are milligrams zinc per gram dry weight.

at a much earlier location in the rat reproductive tract, possibly beginning within the testes itself. It is obvious that preprostatic canine spermatozoa contain much less zinc than the corresponding preprostatic rat spermatozoa. In the rat, epididymal and vasal spermatozoa are rich in zinc and the prostatic fluid constitutes only a small part of the ejaculate. In the dog, on the other hand, preprostatic spermatozoa are extremely poor in zinc and the bulk of the ejaculate consists of prostatic fluid rich in zinc. These facts present evidence consistent with the hypothesis that there is a biological need for zinc in the spermatozoa and that, in the dog, it is a function of the prostate to supply this need. In the rat, apparently, the spermatozoa do not have to depend on the prostate to supply their zinc requirements. Although high levels of zinc are present, Gunn et al have demonstrated that the prostate is not necessary for fertility and fecundity in the rat species (51, 26). Since, in the dog, it has been presumably shown that the greater part of the zinc which is acquired by the spermatozoa is contributed by the prostate, it should now be shown whether this prostatic function is or is not essential to fertility or fecundity in this species. Similar studies, such as the above, have not been done in the human species to date.

Values for prostate gland concentrations of zinc in general tend to run very high. Depending upon the investigator, values range from 102 mg Zn/g dry wt. to 859 mg Zn/g

dry wt. (17, 53).

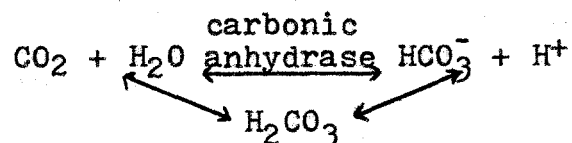
The activity of seminal carbonic anhydrase simultaneously increases with the zinc content, however, the amount of enzyme calculated to be present only accounts for 3.5 percent of the total zinc present (52). Thus, though carbonic anhydrase is present in human semen, its activity is insignificant and can not account for the high zinc content in semen (102 mg Zn per g dry wt. human semen (103)). Neither acid or alkaline phosphatase activities appear to be related to zinc content (21, 33).

6. Blood

Whole Blood. Various investigators report zinc values in whole blood to range from 300 ug to 1500 ug Zn/100 cc (66, 98, 105). Plasma values range between 80 ug and 390 ug/100 cc while red blood cell concentration are reported to be between 690 ug and 1440 ug/100 cc. Should one desire to calculate percentages; 75 to 85 % of the whole blood zinc is contained in erythrocytes, 12 to 22% is contained in serum and 3% is contained in the leukocytes (96, 103). However, the individual leukocyte contains 25 times as much zinc as does the individual erythrocyte (98).

Erythrocytes and Carbonic Anhydrase. Under normal conditions, the entire zinc content in erythrocytes can be accounted for as carbonic anhydrase (36). In 1940, Keilin and Mann reported that the newly isolated, purified

erythrocyte carbonic anhydrase molecule contained 0.33% zinc (42). Carbonic anhydrase is a zinc metalloenzyme that reversibly catalyzes the hydration of carbon dioxide to bicarbonate and hydrogen ions according to the following equations (14):



The enzyme is found in red blood cells, kidney, gastric mucosa and to a lesser extent, the central nervous system, lungs, pancreas and salivary glands (11).

In most normal persons and patients with anemias; (except pernicious anemia) polycythemia vera, secondary polycythemia, leukemia and congestive heart failure, both erythrocyte zinc levels and carbonic anhydrase activity are lowered in parallel fashion, so that the decreases are proportional to the decreases in hematocrit, hemoglobin levels, and erythrocyte counts. In pernicious anemias, the erythrocyte zinc concentration and carbonic anhydrase activity remain nearly normal, although hematocrit, erythrocyte count and hemoglobin levels are markedly decreased. Thus zinc and enzyme values per unit of R.B.C. remain in the normal range in the diseases listed above, whereas, in pernicious anemia, the zinc and enzyme values per unit of R.B.C. are significantly elevated above normal. A similar type relationship exists in sickle cell anemia (99).

Leukocytes. Zinc has been thought to be associated with the granules of polymorphonuclear and eosinophil cells, the eosinophils containing 10 times more zinc than do other leukocytes (55). Indeed, a protein containing 0.3% zinc per gram dry weight has been isolated from human leukocytes. This zinc protein is responsible for 80% of all the zinc found in human leukocytes and is differentiated clearly from carbonic anhydrase. While the protein is presumably an enzyme, the nature of its enzymatic activity is not known (34).

Pihl and co-workers proved zinc to be the principal metal in the granules of eosinophilic granulocytes, and also in the eosinophilic granules of peritoneal mast cells (69, 68). They postulated that the metal may be related to zinc-dependent enzymes like dehydrogenases, amino-peptidase, and phosphatases which occur in eosinophil granules and also in neutrophils and mononuclear leukocytes. An alternative explanation suggested by Mashe would be that zinc here, as in the islets of Langerhans, may have a stabilizing effect on some specific protein (50).

Serum or Plasma. The role of zinc in plasma has not yet been well studied. It would seem quite probable that zinc becomes bound into zinc-protein complexes and metallo-enzymes. What is not excreted or removed from circulation by passage into intracellular compartments, becomes a large pool of readily exchangeable zinc.

"Firmly" and "loosely" bound moieties are present in all serum protein fractions, though zinc seems most strongly bound to the globulins (112). Others have felt that a majority of the zinc is loosely bound to albumin and carried in this fashion (103).

Himmelhoch recently discovered three, hithertofore, new unknown serum zinc proteins. These seem to be "firmly" bound zinc-protein complexes that do not overlap the chromatographic activity profiles of some other zinc-protein complexes found in serum; lactic and dehydrogenase, alkaline phosphatase, carboxypeptidase and glutamic dehydrogenase. These proteins have not yet been characterized (32).

Eminians and others, have suggested normal zinc levels in serum or plasma to be in the range of 90 to 120 $\mu\text{g}/100\text{ cc}$ (17, 103). As will be brought out later in this discussion, a great variety of diseases tend to affect the serum zinc, either increasing or decreasing the levels from the normal.

7. Milk

In cows, the concentration of zinc in milk (3-5 mg/L) is about 10 times greater than that of iron, 100 times greater than that of copper, iodine and manganese, and 1000 times greater than that of cobalt. Similar differences may be found in human milk (96). Colostrum, in all species studied, contains 3 to 5 times the amount of zinc that is found in later true milk. Values as high as 20 mg Zn/L have been

observed in humans at the time of delivery. The zinc level then returns slowly to the normal value (3-5 mg/L) over a 6 month period (3).

Nishimura easily demonstrated zinc deficiency in baby mice, simply by exclusion of zinc-rich colostrum from their diets by fostering them at birth with mothers at later stages of lactation. Newborn mice nursed by their own mothers for $2\frac{1}{2}$ -4 days before transfer to foster mothers, grew normally, whereas newborn mice that were fed, for periods of 3-5 days by foster mothers that had been lactating 13-18 days, and were then returned to their own mothers, usually developed disorders somewhat typical of zinc deficiency which could be prevented by, or which responded to, oral administrations of zinc (63). This phenomenon has not yet been studied in humans.

8. Urine

In consideration of the urine zinc levels and the normal kidney blood perfusion, one could postulate a rather efficient system of tubular reabsorption of zinc. Normal individuals excrete in the urine, relatively small amounts of zinc daily (0.1-0.9 mg/day) (96). Significant zincuria may occur in; Albuminuria, average 2.1 mg Zn/24 hr (20), post-alcoholic cirrhosis, average 1.0 mg Zn/24 hr (101), post-operative period, range 2.8 mg Zn/24 hr initially to 1.3 mg Zn/24 hr on day 20 (31).

9. Bone

Early researchers felt that zinc resembles lead and nickel in its tendency to accumulate in the bones, and they reported relatively high values of zinc for bones and teeth (150-250 ppm) (9, 15, 49).

Day and McCollum in 1940, while studying zinc deficiency in the rat, found a reduction in the proliferative activity of cartilage cells and a decrease in osteoblastic activity, as manifested by a decrease in metaphyseal bone beneath the cartilage plate (12). Prasad, in his initial study of apparent zinc deficiency in human males, found dwarfism to be a part of the clinical picture (72). Zinc is in some way bound to the initiation of mineralization of preosseous tissue and is progressively incorporated within the preosseous tissue as mineralization occurs and it is still present in fully calcified tissue. On the basis of zinc-65 and biochemical studies, it can be said that zinc is literally sequestered in calcified bone and masked for histochemistry and is not available for ionic exchange. It has been postulated that zinc helps to catalyze the calcification process and therefore, is essential to the growth or metabolism of bone though the mechanism has not been established (30).

10. Liver and Pancreas

Zinc, unlike iron and copper, is not normally stored

in large amounts in the liver, in fact, studies with zinc-65 indicate a rapid deposition and high turnover rate in liver, pancreas, kidney, pituitary and adrenals. However, earlier studies have indicated that both liver and pancreas contain approximately twice the amount of zinc contained in other body tissues (67). This seems to be controversial.

Excretion of absorbed zinc from the body largely in the feces, is thought to be mainly by way of the pancreatic secretions which contain a quite high concentration of zinc, probably due to the pancreatic zinc metalloenzyme, carboxypeptidase (103, 58). It has been shown by radioactive zinc studies, that the zinc-65 content of bile is very low (58).

Much early research has been carried on with the pancreas and zinc metabolism due to the once thought possibility of a zinc - insulin interrelationship holding the key to diabetes alleviation (103). However, this has largely been disproven now.

11. Sweat

Prasad and his co-workers, in a study from Egypt, found the zinc content of whole sweat to be 115 ± 30 mg% and that of cell-free sweat to be 93 ± 26 mg%. Thus, in a hot climate where sweating can be excessive, one may lose up to 2 to 3 mg of zinc per day (75). This is thought to be one of the mechanisms causing zinc deficiency in humans.

CHAPTER III

ZINC DEFICIENCY IN HUMANS

1. Etiology and Manifestations of Zinc Deficiency

Up until 1961, when Prasad and co-workers reported on their work in Shiraz, Iran, the possibility of zinc deficiency states in humans had not been widely considered. As previously stated, Eggleton produced evidence of subnormal zinc levels in epidermal structures in beriberi sufferers, however, this was not considered to be zinc deficiency per se (16). Zinc deficiency, as found in Iran and later seen similarly in Egypt, was manifested by what appeared to be a severe iron deficiency anemia in conjunction with arrested growth, hepatosplenomegaly and hypogonadism in young male adults (73, 74).

The conclusion that these patients were manifesting zinc deficiency is based upon the following: (a) the zinc concentrations in plasma, red blood cells and hair were decreased as compared to normal subjects; (b) the excretion of zinc in urine and sweat was decreased; (c) the radioactive zinc-65 studies which revealed that the plasma zinc-turnover rate was greater in the patients, the 24-hour exchangeable pool was smaller, and the excretion of zinc-65 in stool and urine was less in the dwarfs than the control subjects (74).

The possible factors responsible for zinc deficiency in these subjects are several; (1) Poor availability of zinc

from the diet normally consumed in the villages of Iran and Egypt; either low content of zinc or zinc being complexed by high levels of phytate in the bread and beans of the diet. Phytate being a strong complexer of zinc. (2) Blood loss caused by hookworm or schistosomiasis infestation. (3) zinc lost by excessive sweating (74).

The anemia in all cases was hypochromic, microcytic in type and related to iron deficiency and was completely corrected by oral administration of iron salts. However, the administration of iron salts did not correct the hepatosplenomegaly or alleviate the growth retardation or hypogonadism. This would seem to indicate severe anemia and iron deficiency are not necessary factors for growth retardation and hypogonadism (76).

No evidence for deficiency of other essential trace elements or vitamins were obtained (76).

In all cases, following treatment with zinc, the size of the liver and spleen decreased markedly. The rate of growth increased and was greater in patients who received supplemental zinc as compared to those who received iron instead or just plain hospital diets. Pubic hair appeared in all cases within 7-12 weeks after zinc supplementation was started. The genitalia size became normal and secondary sexual characteristics developed within 12-24 weeks in all cases which received zinc. On the other hand, no such changes

were observed in the iron supplemented group or on hospital diet alone in the comparable length of time. Two dwarfs which refused to take part in the study were followed in their villages for 1 year. They failed to grow or show any changes in their sexual development (76).

Liver function tests were all unremarkable, except for the serum alkaline phosphatase which increased to normal levels following treatment (73).

2. Absorption and Excretion

Like iron, zinc appears to be absorbed only to a limited extent from the intestine. Studies using zinc-65 have shown that only 5 to 10% of dietary zinc is absorbed at a normal intake level (67). Since the average well balanced human diet supplies 10 to 15 mg. of zinc per day, the daily intestinal absorption has been estimated to be 0.5 to 1.5 mg zinc per 24 hour period (19). The site of absorption of zinc from the intestine and the mechanisms involved are not understood at the present time (67). No specific plasma protein has been definitely identified as a transport protein for zinc, as is true in the case of iron (transferrin), and of copper (ceruloplasmin), but some think that zinc may combine with the β globulin, transferrin, noncompetitively with iron and thus this protein be responsible for the transport of both iron and zinc in the body (106).

O'Dell and Savage have shown that phytic acid, found at high levels in some grains and vegetables, decreases the absorption of zinc similar to its effect on the absorption of iron (65, 64). Also, high levels of calcium and phosphate have been reported to inhibit intestinal absorption of zinc. Geophagia or clay eating, (clay containing increased levels of phosphate) has been suggested as one of the contributory factors in the patients described from Shiraz in 1961 (73). The pH of the diet, or of the intestinal tract, or both, may also influence the availability of zinc (60).

Most of the zinc intake is excreted unabsorbed in the stool, chiefly, as stated above, in the pancreatic secretions and a small amount in the bile (61). Compared with the amounts ingested, the amount of zinc excreted in the urine of normal individuals are exceedingly small, on the order of 0.1-0.9 mg. per day. Zinc excretion appears to be independent of the urinary volume (34). However, as will be taken up later, urinary zinc levels may be quite elevated in certain disease states.

3. Endocrine Manifestations

Sandstead and his co-workers (84, 85), working with Egyptian dwarfs, apparently zinc deficient, similar to those reported upon by Prasad (74, 75), masterfully studied with rather involved research, the endocrine manifestations of those dwarfs.

Noting that zinc apparently concentrates to some extent in the pituitary (45), and that pituitary gonadotropin (57) and corticotropin (35) are apparently augmented by zinc in experimental animals, and observing some of the cardinal manifestations of panhypopituitarism in the dwarfs, (arrested growth and osseous development though normally proportioned bodies, hypogonadism, depressed ACTH production, and increased sensitivity to insulin), they studied various parameters of endocrine function in these dwarfs (29).

Linear growth, bone age, thyroid function, glucose tolerance, pituitary corticotropin reserve, adrenal cortical function and pituitary gonadotropin excretion were evaluated by standard techniques.

Each child, after preliminary evaluation, was treated either by diet alone or with supplementation of either iron (1 gm/day) or zinc (90 mg/day) and followed for a long period of time. Controls were included which used their normal diet, but with or without supplementation with iron or zinc.

Patients receiving iron gained in height, but the increase was not as striking as the growth acceleration in those receiving zinc. Two patients originally given iron were subsequently given zinc and an additional growth increase occurred. The plasma zinc concentration of these patients receiving iron approached normal, (the zinc source presumably the diet), though in some cases the serum iron

concentration remained low. The zinc supplemented group had a growth acceleration despite the continued presence of low hemoglobin and serum iron concentrations. Neither of the two village controls who received no micronutrient therapy, grew during the observation period (greater than 300 days).

Overt hypothyroidism was not present and the pituitary-thyroid interactions were generally normal. The majority had normal PBI's and normal to elevated 24 hr RAT uptakes. Serum cholesterol was low.

Liver function tests were normal in nearly all patients, and liver biopsies were done, though there was no evidence grossly or microscopically of fat malabsorption. The D-xylose absorption test was normal.

A variety of abnormal curves were obtained in the oral glucose tolerance test with the majority of patients having an apparent delayed absorption of glucose. Relatively prolonged elevations in blood sugar occurred in others.

Intravenous glucose tolerance tests were normal to slightly accelerated in nearly all patients indicating adequate insulin production. Three out of the four patients tested, using the Engel-Scott insulin-glucose test (18), showed striking intolerance to intravenous insulin (0.1 units regular insulin/Kg body weight) requiring termination of the test but indicating hypopituitarism in these patients.

The responses to exogenous adrenocorticotropin (ACTH)

and Metopyrone infusion test were frequently abnormal. The mean basal 17-hydroxysteroid (17-OHS) excretion was 6.24 ± 2.6 mg/24 hr. After ACTH stimulation, (40 units IV in D5W, given over 8 hours, beginning between 8 and 10 A.M. on 3 consecutive days), the rise in urinary 17-OHS was frequently delayed, or following an initial rise, there was a fall on successive days. These findings suggested a decreased adrenal reserve, possibly secondary to decreased ACTH production or release.

The excretion of 17-OHS following the Metopyrone infusion test was subnormal in the majority of patients, both in terms of absolute rise in 17-OHS excretion and in comparison to the ACTH response.

The responses to intravenous Metopyrone coupled with the ACTH tests suggest the presence of limited pituitary ACTH reserve.

After periods of treatment with zinc, iron, or diet, the pituitary-adrenal axis was re-evaluated, in six patients, and showed an improved response to ACTH in four patients, but the response to Metopyrone infusion improved in only one. Although the number of observations were too small to obtain valid conclusions as to the cause of improvement, their data suggested that increased response from ACTH and Metopyrone was associated with improved zinc nutrition and was not dependent upon iron.

Hypogonadism in the group of patients was manifested by absence of pubic, axillary or facial hairs, a small penis and atrophic testes (prepuberant sexual development). Urinary pituitary gonadotropins and 17-Ketosteroids were low in all patients with the average 17-Ketosteroid excretion for the group approximating the normal level for eleven year old children.

Diet and iron therapy were followed by slow maturational changes. In contrast, treatment with zinc was followed by surprisingly accelerated sexual maturation. In some, pigmented pubic, extremity, and facial hair appeared within 3 weeks of beginning of zinc treatment and maturational changes in the penis and scrotum could be seen. Early growth of pubic and lip hair was followed by an increase in genital size, the growth of additional facial, extremity, pubic, and finally, axillary hair. Urinary excretion of pituitary gonadotropin also became normal in some patients. The two untreated control patients remaining in the village, did not show change in genital size or development of secondary sexual characteristics during the observation period of greater than 1 year.

The endocrine abnormalities in this group of patients are compatible with hypopituitarism. In this group, growth failure and hypogonadism are the most outstanding features, but also, decreased pituitary ACTH reserve and an abnormal

oral glucose tolerance have been found. Here, hypothyroidism did not appear to be an obvious problem, however, the thyroid studies did suggest iodine deficiency in some cases.

Zinc therapy caused an improvement in these clinical features and apparently induced puberty. Diet and iron therapy alone, while tending to alleviate somewhat, did not bring about a marked improvement in the symptoms.

It is probably still a little soon to denote a cause and effect relationship between zinc deficiency and hypopituitarism, since all the evidence is not yet in, but indications and evidence is certainly in that direction.

CHAPTER IV

BIOCHEMICAL ASPECTS OF ZINC METABOLISM

1. Zinc Metalloenzymes

Continued research in the past few years seems to make it clearer that most micronutrients function through their relationship with enzymes, hormones, nucleic acids, and other proteins. Although zinc has been studied in living organisms for many years, it has only been recently that one can presume the manner of zinc participates in metabolism. Its relationship with enzymes has been a center of recent biochemical research in the field.

Although Keilin and Mann reported the isolation of carbonic anhydrase in 1939, it has only been recently that

the impetus of study has mushroomed into the discovery of some twenty zinc-containing metalloenzymes from a great variety of species. This would seem to indicate an overall importance of this element in metabolism (93). See Table (2).

"The zinc atoms in these molecules are specifically and firmly incorporated into the protein such that they can be thought of as a single physical entity in their native state. Thus, during isolation of the enzyme, the ratio of zinc to protein rises to a fixed limit, as does the ratio of activity to protein. As a result, the ratio of zinc to activity also reaches a fixed limit, while the ratio of the sum of all other metals to activity simultaneously approaches zero. With complete purification, the number of gram atoms of zinc per mole of apoenzyme is an integral value, attesting to the specificity of the association and implying stoichiometry. The concomitant rise of zinc with activity suggests that the metal is specifically and critically related to enzymatic function. In this regard, these characteristics of zinc metalloenzymes contrast with those of zinc-metal-protein complexes, a large group of enzymes which may require zinc as one of several metals for activity, but which cannot be isolated with a metal in situ, due to the weaker and less specific association between it and the protein (104)".

Carbonic Anhydrase. First reported as a CO₂-protein catalyst in 1932, this enzyme has been found in a number of

TABLE 2.
ZINC METALLOENZYMES

Enzyme	Source
Alcohol dehydrogenase	Yeast
Alcohol dehydrogenase	Equine liver
Alcohol dehydrogenase	Human liver
Lactate dehydrogenase	Rabbit muscle
Malate dehydrogenase	Porcine heart
D(-) Lactate-cytochrome C reductase	Yeast
D-Glyceraldehyde-3-phosphate dehydrogenase	Rabbit and bovine muscle
D-Glyceraldehyde-3-phosphate dehydrogenase	Yeast
Glutamate dehydrogenase	Bovine liver
Alkaline phosphatase	E. coli
Alkaline phosphatase	Mammalian kidney
Alkaline phosphatase	Human leukocytes
Carboxypeptidase A	Bovine pancreas
Carboxypeptidase B	Porcine pancreas
Carboxypeptidase B	Bovine pancreas
Neutral protease	B. subtilis
Aldolase	Yeast
Aldolase	Aspergillus
Carbonic Anhydrase	Bovine erythrocytes
Carbonic Anhydrase	Human erythrocytes

organisms including plants, cattle, sheep, and humans. In erythrocytes, it acts as a catalyst to mediate CO_2 excretion from the body. It is thought to have a molecular weight of 30,000 and contains a zinc concentration ranging from 0.2% to 0.3% depending upon its source. The chemical details of the bonding between zinc and the protein are not known, neither also is the mechanism of its action known (103).

Alkaline Phosphatase. This enzyme has been isolated from kidney, *E. coli*, and human leukocytes. It is thought to contain 0.15% of firmly bond zinc with several metal binding sites per each molecule enzyme (103). Prasad found depressed levels of alkaline phosphatase which reverted to normal by zinc supplementation (73).

Lactic Dehydrogenase. Apparently an NAD-dependent enzyme, first isolated from rabbit skeletal muscle, this enzyme has not been completely characterized but seems to catalyze the redox interconversion of lactic and pyruvic acids (103).

Glutamate Dehydrogenase. Also a NAD-dependent enzyme, this enzyme is different from other dehydrogenases by not acting on primary or secondary alcoholic groups, but which catalyzes the reversible oxidative deamination of an amino acid. It is thought to have a molecular weight of 1,000,000; a much larger molecule than other pyridine nucleotide-dependent enzymes (103).

Carboxypeptidase. First purified from pancreatic juice, this enzyme has a molecular weight of 34,000. Each molecule contains one atom of zinc. When zinc is removed from the enzyme, activity is lost in direct proportion. Readdition of zinc ions fully restored activity (102, 103).

Its main function is to catalyze the hydrolysis of carboxy terminal peptide bonds in proteins and peptides, but it also hydrolyzes esters. While enzymatic activity may be restored to the apoenzyme in varying degrees by the addition of other metals, these metals do not give the complete spectrum of specificity of action that is attained by the native zinc enzyme (93).

Hsu, studying zinc deficiency in rats, reported that it caused decreased activity of pancreatic carboxypeptidase B or liver alcohol dehydrogenase. The observed reduction of enzymic activity may be related to poor proteolysis in the intestinal tract and therefore, poor utilization of feed which occurs in zinc deficient rats (37).

Alcohol Dehydrogenase. Isolated from yeast as early as 1937, this enzyme has also been found in liver of various species, and is thought to present zinc atoms as an active enzymatic site with an unexplained interaction between NAD and alcohol dehydrogenase. Thus, this enzyme also is apparently a NAD-dependent enzyme whose concentration and, or, activity varies directly with the activity of NAD (103).

One function that has been studied is the conversion of vitamin A alcohol to vitamin A aldehyde in the process of vision. The essentiality of zinc to this enzyme can be seen, as mentioned earlier, by causing blindness in dogs due to binding of zinc by chelating agents.

Evidence seems to indicate formation of enzyme-coenzyme-substrate complex with the zinc atom functioning at or in close proximity to the active site on the enzyme molecule (93).

2. Zinc-Enzyme Complexes

In addition to being a necessary constituent of a number of metalloenzymes, zinc functions as a co-factor, apparently increasing in some nonspecific manner the activity of a number of other enzymes. These include arginase, carnosinase, lecithinase, enolase, aldolase, oxaloacetic decarboxylase, alkaline phosphatase, histidine deaminase and a number of mono-, di-, and tri-peptidases (103, 93).

CHAPTER V

ZINC RESEARCH IN DISEASE PROCESSES

Current literature is beginning to show important and significant reports of promising research on zinc as it is related to disease processes and basic cellular metabolism. These will be briefly summarized.

1. Post-Alcoholic Cirrhosis and Hepatitis

It has been previously stated that zinc is an essential component of several hepatic enzymes, including glutamic and alcohol dehydrogenases. Several investigators (103, 106, 23) have reported a decrease in serum zinc levels in patients with post-alcoholic cirrhosis. Vallee (103) reported abnormally high urinary zinc excretion in these patients, in the order 1000 ± 200 ug per 24/hrs. The abnormal variance of zinc levels in these patients tends to correlate positively with the severity of the disease. Liver tissue zinc concentrations were decreased below normal levels.

Since zinc is an essential component of the enzyme, liver alcohol dehydrogenase, and therefore, participates in the oxidation of alcohol, and since ethanol is considered to have an etiologic role in the development of Laennec's cirrhosis, it follows that low zinc levels in the body may play some role in the development of alcoholic cirrhosis. This has been substantiated by Vallee (103) to the extent that the oral administration of zinc quickly resolves these abnormalities of zinc metabolism thus suggesting a "conditioned" zinc deficiency, and producing a tendency toward restoration of normal liver function. Whether or not this also produces a reversal or termination of the cirrhotic process has not as yet been determined or substantiated. It has been suggested by studies that following alcohol

ingestion, the serum zinc concentration decreases (91). Similar results have been reproduced by Kahn and co-workers, in carbon tetrachloride induced liver cirrhosis of rats (40).

It has been proposed that high blood levels of alcohol could diminish the activity of zinc containing alcohol dehydrogenase and result in its degradation with increased zinc excretion (100).

The tendency to low serum zinc concentrations in cirrhosis could be regarded as a manifestation of zinc deficiency or it could be the result of low levels of zinc-carrying protein.

Bilirubin inhibits trypsin, chymotrypsin, pancreatic amylase and intestinal alkaline phosphatase (1, 90). Fletman suggests bilirubin may do other than chelate zinc and may bind protein or inhibit enzyme systems not containing zinc. In vitro reversal of bilirubin inhibition can be achieved by addition of zinc sulfate. There may be related cause and effect in advanced Laennec's cirrhosis with low serum zinc levels and increased urinary excretion of zinc and decreased levels of hepatic alcohol dehydrogenase as have been reported above in Laennec's cirrhosis. Since hyperbilirubinemia is often present in last stages of post-alcoholic cirrhosis, bilirubin may promote excretion of zinc as a bilirubin-zinc chelate. This hyperbilirubinemia has not yet been correlated with zincuria (22).

Kahn and co-workers found a tendency to an elevated serum zinc in acute hepatitis, which they felt could be a result either of release of zinc containing enzyme from damaged hepatic cells or of an increase in zinc binding protein owing to its release from the liver, analogous to the elevation of serum iron found in acute hepatitis. They also noticed an abnormally high urinary zinc in half of their patients (39).

2. Respiratory Distress Syndrome

An interesting side aspect to zinc-enzyme complex interaction may be found in respiratory distress syndrome of premature infants and zinc-carbonic anhydrase activity. In a study made by Kleinman, normal, full term, newborn infants had approximately 25% of the carbonic anhydrase activity of adults. Premature infants without respiratory distress syndrome, average 13% of adult enzymatic activity and those infants with respiratory distress syndrome average 5% of adult activity (44).

The enzymatic activity from premature infants with the syndrome were significantly lower (P less than 0.001) than the activities from premature infants without the syndrome. See Table (3).

Newborn babies have blood zinc levels much lower than normal adults, but there is no significant difference in blood zinc between prematures with and prematures without

TABLE 3.
 COMPARISON OF CARBONIC ANHYDRASE AND ZINC LEVELS
 IN ADULTS, FULL-TERM NEWBORN INFANTS, AND
 PREMATURE INFANTS WITH AND WITHOUT
 RESPIRATORY DISTRESS SYNDROME

Subjects	Number	Carbonic Anhydrase E.U./ml	Zinc µg/ml	Ratio of Carbonic Anhydrase to Zinc Concentration E.U./µg
Adults	15	4429 ± 100	5.45 ± 0.18	820.0 ± 19.5
Full Term Newborn Infants (40 or more wk gestation)	76	1100 ± 56.0	1.77 ± 0.06	602.5 ± 28.4
Premature infants (40 wk gestation) without respiratory distress syndrome	26	584 ± 62.0	1.47 ± 0.07	449.5 ± 38.4
Premature infants (40 wk gestation with respiratory distress syndrome	19	234 ± 22.6	1.59 ± 0.12	166.1 ± 24.7

respiratory distress syndrome. Thus, the enzymatic activity per microgram zinc was considerably and significantly lower ($P < 0.001$) in the premature infants who had the syndrome.

Kleinman postulates perhaps one of the carbonic anhydrase isoenzymes found at low levels in adult blood are at high levels in fetal blood. Tappan et al have shown that newborn red blood cells have lower carbonic anhydrase specific activities than adult red cells (92). Kleinman further suggests that a change of low specific activity to high specific activity carbonic anhydrase occurs with maturation and that this change is slowed or altered in infants with the respiratory distress syndrome.

3. Skin Diseases

Significantly lowered plasma-zinc concentrations were found in patients with psoriasis, other dermatoses and venous leg ulcerations. See Table (4). This finding of abnormally low zinc concentrations in the plasma of patients with widely differing dermatoses suggests that similar non-specific mechanisms may be responsible (24).

A study done by Kozlowski and associates, unfortunately without statistical controls, found a decrease in the zinc content in granulocytes in patients with advanced skin neoplasia, patients with non-specific skin diseases but with coexistent internal malignancy, patients with disorders of the lympho-reticular system and in patients with psoriasis

TABLE 4.
ZINC CONCENTRATIONS IN PATIENTS WITH SKIN DISEASES
AND IN HEALTHY CONTROLS

Subjects	Number	Age (yr) (Mean & Range)	Mean Plasma Zinc (UM)	Standard Deviation
Controls	41	30.6(19-64)	18.1	1.92
Psoriasis	20	48.3(19-64)	15.5	2.49(p<0.001)
Ichthyosis	10	35.1(16-63)	16.5	2.43(p<0.05)
Chronic Venous Leg Ulcers	9	58.4(51-61)	15.4	1.71(p<0.001)
Other Skin Diseases*	13	45.5(15-61)	15.4	2.39(p<0.001)

*DIAGNOSIS: Lichen planus (3), eczema (3), urticaria (2), scleroderma (1), pemphigoid (1), dermatitis herpetiformis (1), rosacea (1), chronic discoid lupus erythematosus (1).

P = significance of difference between test and control means.

and erythrodermia (46).

4. Thermal Burns

A number of complex metabolic alterations occur as the result of full thickness thermal burns. Since approximately 15% to 20% of the body zinc store is normally found within the skin, alterations in zinc metabolism might be expected to occur in thermal burn patients.

Henzel reports a marked body zinc deficit with an initial sharp loss of zinc following severe thermal burns in over forty patients which lasts up to 2 to 3 months following the injury before reverting to normal (31).

Although the skin is a large reservoir of zinc storage, an alternative reason for the zinc deficit and urinary loss must be found beyond stating the thermal burn is the etiology of the loss since zinc stores in a full thickness burn should theoretically be lost to body use since the burn site is no longer blood perfused tissue. This has not yet been explored.

5. Wound Healing

Acceleration of normal healing by dietary zinc supplementation was accidentally discovered in rats in 1955 by Strain (88). It, however, was not until 1967 that successful implementation of this finding was reported in humans (70).

Comparative studies of wound healing were made with and without oral zinc sulfate therapy in young human male

subjects by measuring the rate of wound healing in wounds formed by pilonidol-sinus tract excisions that were allowed to heal by secondary intention. The rate of healing was determined by measurements of wound volumes and the number of days for complete repair. Patients in the treated group were given 150 mg of elemental zinc daily in the form of zinc sulfate in addition to normal diet. Patients in control group were given no medication other than normal diet.

As can be seen in Table (5), the healing rates (ml. per day) were nearly three times greater in the treated group as compared to the control subjects. Although the experimental group had wound volumes much larger than those in the control group, the larger wounds healed 43% sooner with orally administered zinc sulfate (71). Although the medicated group healed more rapidly throughout the course of the trial, differences were small during the first fifteen days.

Of further significance was the difference in wound appearance between the two groups. Wounds in the patients on zinc sulfate therapy had cleaner, pinker and healthier granulations with considerably less purulent exudate than wounds in the control group.

Healing of the granulating wounds could be correlated with the concentration of zinc as measured by hair analysis (70).

Savlov et al reported in 1962 that radioactive zinc

TABLE 5.
 COMPARISON OF MEANS OF WOUND VOLUMES, DAYS FOR COMPLETE HEALING,
 AND HEALING RATES IN UNTREATED CONTROL PATIENTS AND
 PATIENTS TREATED WITH ZINC SULFATE

	Age (yr)	Wound Volume (ml)	Days for Complete Healing	Healing Rate (ml/day)
Mean of Control Patients	25.0	32.3	80.1 ± 13.7	0.44 ± 0.09
Mean of Treated Patients	24.6	54.5	45.8 ± 2.6	1.25 ± 0.30
Significance	—	—	p<0.02	p<0.01

is preferentially concentrated in healing tissues with the peak of activity during the first days after injury, followed by gradual decrease. But migration of zinc into wound appears to be temporary since at the time of complete scarring, one hundred days after injury, zinc-65 was not detected in the scar, although the radioisotope was still measurable in most tissues (86).

6. Post-operative Zincuria

As evidence seems to be accumulating that zinc levels may become depressed following significant stress or trauma to the biologic organism, man included, surgeons could anticipate the zinc levels to be affected by operative trauma. Indeed, this seems to be the case. Henzel reports significant increases in 24 hour urinary excretion of zinc (which reflects acute changes in biologic zinc stores) following operative procedures as compared to non-operated controls (31). Twenty-four hour urinary excretion of zinc averaged 0.70 mg/day in the control patients as compared to 1.28 mg/day urinary excretion of zinc during the 20-day postoperative observation period. During the first three postoperative days, daily losses as high as 2.8 mg were recorded per the 24-hour collection periods.

While postoperative zincuria may not represent a problem in the normal healthy operative patient, it could significantly tilt the balance of zinc stores and cause

further depletion in those patients with borderline or sub-normal stores and cause a tendency to delayed or resistant wound healing.

Consideration should be given to possible zinc supplementation in those patients presenting delayed wound healing.

7. Malignant Diseases

The status and role zinc may play in neoplastic disease either as an etiology or a therapeutic role remains at best sketchy and contradictory with probable multiple factors contributing to the confusing state.

Vallee (103) reports a number of authors who have studied zinc in relation to neoplasm. They need not be repeated here.

Erythrocyte zinc levels in myeloproliferative disorders were studied by Valberg who also reports a number of other contradictory authors on zinc status in hemoplastic diseases (97). Valberg found erythrocyte zinc to be increased above normal in all diseases studied, but significant to $P < 0.05$ only in acute leukemia, chronic lymphatic leukemia, chronic myelogenous leukemia, Hodgkin's disease, and metastatic carcinoma. The greatest increase in mean zinc levels was present in chronic myelogenous leukemia and Hodgkin's disease, the smallest increase in chronic lymphatic leukemic and values intermediate between these results

were found in acute leukemia, multiple myeloma and in carcinoma. The values in this study are in accord with certain previous observations.

Reduced levels of zinc in granulocytes, in contrast to above reported increased erythrocyte zinc levels, are reported by Lawkowicz in patients with wide range of neoplastic diseases (47). However, values of granulocyte zinc are reported above normal in chronic lymphatic leukemia.

Alterations of zinc levels in tissues which presumably are not directly participating in the neoplastic process, suggests a generalized disorder of zinc metabolism.

Changes in the activity of certain enzymes have been reported in normal and tumor tissues of tumor-bearing animals and man (25, 10). Rosoff suggests that since the activity of some enzymes depends upon the presence of specific trace metals, cellular derangements resulting in neoplasia may be linked with changes in trace metal concentration (82).

Conjecture concerning the role of zinc in neoplastic disease may be premature at this time.

8. Benign Prostatic Hypertrophy and Prostatic Carcinoma

The in vivo concentration of zinc in human prostatic tissue is low in cancer and very high in hyperplasia as compared to normal prostatic tissue (27). This relationship is inverse in the in vitro situation. Probably this is an

expression of the in vivo saturation of zinc binding sites in the hyperplastic tissue and the relatively unsaturated sites in carcinomatous prostatic tissue (28). Gyorkey hypothesizes a zinc-chelation phenomenon in BPH and a depression of leucine amino peptidase levels, a zinc metallo enzyme in prostatic carcinoma (27).

9. Myocardial Metabolism and Cardiovascular Disease

It has been known for several years that a significant decrease in serum zinc is observed in myocardial infarction with levels averaging 67 ± 13.8 μg zinc per 100 cc as compared to 120 ± 19.0 μg zinc per 100 cc in normal control patients (109). This is accompanied by changes in a variety of enzymes activities and an increase in copper concentration (108).

Following the ingestion of oral alcohol, it has been found that zinc is liberated from the myocardium. In peripheral venous studies of alcoholic patients, as zinc levels fell, alcohol dehydrogenase activity rose, suggesting a relationship between the changes in zinc and alcohol dehydrogenase (110). Similar observations have been made in myocardial infarction, where a decrease in plasma zinc concentration is accompanied by an increased activity of malic dehydrogenase and lactic dehydrogenase (109). The explanation for the decrease in serum zinc levels and concomittant rise in enzyme activity remains unclear, but it does not

necessarily indicate an increase in enzyme concentration but may be an increase in enzyme activity.

Hair zinc levels were observed to be decreased below normal patients in patients with proven atherosclerosis. The median zinc level of hair was 62 ppm, which contrasted sharply with the provisional normal of 125-150 ppm (89). This is consistent with a previous report by Volkov, who found a significant decrease in the zinc content of plasma, aorta, liver, myocardium and pancreas in a large group of patients with atherosclerosis (107).

10. Zinc Toxicity

Excess zinc ingestion produces an acute and transitory illness within a few minutes after ingestion with the symptoms including malaise, dizziness, tightness of the throat, emesis, colic and diarrhea. Usually, this can be attributed to the preparation of acid foods (fruits, juices, stewed fruits, in galvanized containers, resulting in solubilization of zinc. Treatment is symptomatic and supportive (103).

Zinc poisoning may occur as a result of three distinct processes: (1) ingestion of toxic amounts of zinc with food or drink; (2) direct skin contact with zinc or zinc salts; (3) inhalation of fairly high concentrations of freshly formed zinc oxide fumes (103).

Metal fume fever caused by the inhalation of zinc

oxide fumes results in fever, malaise, and depression and a cough which may become violent enough to induce vomiting, excessive salivation, headache, and possible gastrointestinal symptoms, though this is disputed. Other aspects observed are leukocytosis and chilling about eight hours after exposure (103).

Zinc apparently antagonizes either the absorption of copper from the gastrointestinal tract or the utilization of copper within the tissues or both. Under conditions of excess zinc, there is a breakdown in the mechanism of hemato-
poiesis and of formation of active cytochrome oxidase and catalase, for both of which adequate concentrations of available copper are necessary (96).

The level of zinc toxicity has not been determined in humans. However, the dose of the salt, zinc sulfate, causing emesis is approximately two grams. Pories in his wound healing study, was able to give his patients 220 mg zinc sulfate T.I.D. with impunity, in fact, actual beneficial effects (71).

11. Miscellaneous

On the basis of some research in zinc deficient chicks, an etiology for the development of rheumatoid arthritis could be postulated (62).

Increased amounts of zinc are excreted in the urine of patients with acute intermittent porphyria. Fecal and urinary porphyrins extracted in this condition apparently are

zinc complexes. Zinc may act as a detoxifying agent increasing the water solubility and urinary excretion of the porphyrins (67).

Zinc content of mouse dystrophic gastroneimous is 2.2 times that of normal (38).

Red cell zinc content in patients with pernicious anemia is increased over normal, but reverted to normal levels after therapy (99).

Serum zinc concentrations in acute and chronic infections (pneumonia, bronchitis, erisepelas, pyelonephritis) are decreased below the range of normal values and are restored to normal levels with recovery (76).

Urinary zinc excretion is increased in acute rheumatic fever (67).

Serum zinc levels are increased above normal in hyperthyroidism, hypertension, polycythemia vera, and eosinophilia, and following the administration of adrenaline, thyroxine, thyrotropic hormone, therapeutic X-irradiation and experimentally induced hyperthemia (76).

Increased urinary excretion of zinc has been found in hypertensive patients and during the administration of EDTA. The parenteral administration of disodium calcium EDTA to hypercholesterolemic patients not only produced a significant fall in serum cholesterol levels, but induced a simultaneous tenfold increase in urinary zinc levels, whereas

oral administration produced no consistent changes in the cholesterol levels but more than a fourfold increase in urinary zinc (76).

Evidence seems to indicate that one of the actions of zinc is in the area of protein and nucleic acid synthesis. Zinc deficiency in some micro-organisms interferes with the synthesis of RNA and thus secondarily inhibits the synthesis of DNA and other proteins (77).

CHAPTER VI

CONCLUSION

Much remains to be elucidated concerning the role zinc plays in metabolism of humans. The essentiality of zinc for life has been established and that it is active as the metal moiety of a number of important enzymes. Zinc participates in enzymatic pathways of metabolism through its close association with these enzymes.

The metabolic role of zinc is wide reaching. Homeostatic derangement of zinc produces many different manifestations in plants, animals, and man.

Although dietary intake and biologic stores of zinc may be adequate during health, evidence is accumulating that a deficiency may occur rapidly in the chronically ill or severely traumatized patient. Possibly, supplemental zinc should be provided patients who are nutritionally depleted,

or who have been subjected to severe trauma.

To fully understand the underlying basis and pathology of zinc deficiency and zinc metabolism, it will require continued research to identify the specific areas of metabolic dysfunction and to further delineate observations in the composition and structure of the specific substances which function in association with zinc.

In conclusion, rather than being a micronutrient, or "trace element", as zinc is so often labeled, I submit that zinc is actually a major element absolutely essential to human life, but is only found in small quantities in the body due to the finely tuned role it plays in the overall scheme of human metabolism. There are many unanswered questions remaining to be studied and answered before the complete role of zinc in the body can be fully known.

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