Current Status of Zinc Deficiency in the Pathogenesis of Neurological, Dermatological and Musculoskeletal Disorders*

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ABSTRACT

Recent clinical and experimental studies suggest that zinc deficiency may play an important role in the pathogenesis of (1) acrodermatitis enteropathica, and in certain cases of (2) hypogonadal dwarfism, (3) congenital malformations, (4) hypogeusia and hyposmia, (5) nyctalopia and (6) impaired wound healing. Disturbances of zinc metabolism also occur in a broad spectrum of other clinical disorders. The pathophysiological factors which are responsible for hypozincemia include: (1) nutritional deficiency and/or intestinal malabsorption of zinc; (2) hyperzincuria secondary to aminoaciduria; (3) hormonal effects (cortisol, growth hormone, estrogens); (4) hypoalbuminemia; and (5) effects of leukocytic endogenous mediator. The clinical diagnosis of zinc deficiency in patients with specific neurological, dermatological and musculoskeletal disorders is complicated by the complex interactions of these pathophysiological factors and by the need for more dependable laboratory indices of zinc deprivation.

Introduction

During the past decade, advances in knowledge of zinc metabolism have greatly enhanced the clinical applications of zinc analyses for the diagnosis of human diseases. Several authoritative reviews have been published on the clinical pathology of zinc. In a recent paper, the present author has summarized methods for zinc analysis in biological materials by atomic absorption spectrometry and has tabulated normal values for zinc in human serum, plasma, and urine. In the present paper, attention has been focused upon (1) recent discoveries which have implicated zinc deficiency in the pathogenesis of specific neurological, dermatological and musculoskeletal disorders, and (2) recent investigations which have identified pathophysiological factors that affect zinc metabolism in man.

Acrodermatitis Enteropathica

Within the past year, Moynahan has reported that acrodermatitis enteropathica (Danbolt's disease) may be a genetically
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determined disorder of zinc metabolism. Acrodermatitis enteropathica was described in 1943 by Danbolt and Closs, and the clinical and pathological features have been delineated by numerous investigators. In brief, acrodermatitis enteropathica is a lethal, autosomal, recessive trait which usually occurs in infants of Italian, Armenian or Iranian lineage. The disease is not present at birth, but typically develops in the early months of life, soon after weaning from breast feeding. Dermatological manifestations include progressive bullous-pustular dermatitis of the extremities and the oral, anal and genital areas, combined with paronychia and generalized alopecia. Infection with *Candida albicans* is a frequent complication. Ophthalmic signs may include blepharitis, conjunctivitis, photophobia and corneal opacities. Gastrointestinal disturbances are usually severe, including chronic diarrhea, malabsorption, steatorrhea and lactose intolerance. Neuropsychiatric signs include irritability, emotional disorders, tremor and occasional cerebellar ataxia. The patients generally have retarded growth and hypogonadism. Prior to the serendipitous discovery of diiodohydroxyquinolone therapy in 1953 by Dillaha and coworkers, patients with acrodermatitis enteropathica invariably died from cachexia, usually with terminal respiratory infection. Although diiodohydroxyquinolone has been used successfully for the therapy of this condition for 20 years, the mechanism of drug action has never been elucidated. It now seems possible that the efficacy of diiodohydroxyquinolone might be related to the formation of an absorbable zinc-chelate, inasmuch as diiodohydroxyquinolone is a derivative of 8-hydroxyquinoline, a chelating agent.

In 1973, Moynahan and Barnes studied a two-year-old girl with severe acrodermatitis enteropathica who was being treated with diiodohydroxyquinolone and a lactose-deficient synthetic diet. The clinical response to this therapy was not satisfactory, and the physicians sought to identify contributory factors. They found that the concentration of zinc in the patient’s serum was profoundly reduced and, therefore, they administered oral ZnSO₄. The skin lesions and gastrointestinal symptoms cleared completely, and the patient was discharged from the hospital. When ZnSO₄ was inadvertently omitted from the child’s regimen, she suffered a relapse which promptly responded when oral ZnSO₄ was reinstituted. In their initial reports, Moynahan and Barnes attributed zinc deficiency in this patient to the synthetic diet. However, Moynahan later recognized that the dermatitis and alopecia in acrodermatitis enteropathica were similar to the dermal lesions which had been reported in zinc-deficient rats, and he began to suspect that a genetic abnormality of zinc metabolism might be fundamental to the pathogenesis of acrodermatitis enteropathica. Moynahan tested this hypothesis by administration of ZnSO₄ to nine additional patients, while completely withdrawing diiodohydroxyquinolone from their therapeutic regimens. All of the children became completely free of symptoms, and the prepubertal children experienced rapid increase in rate of growth. The dramatic therapeutic efficacy of ZnSO₄ in acrodermatitis enteropathica has been independently confirmed by Portnoy and Molokhia and Michaelsson. Studies of the metabolism of Zn need to be performed in patients with acrodermatitis enteropathica in order to elucidate the metabolic defect. It may be speculated that these subjects could be genetically deficient in the soluble zinc-binding protein which has been isolated from rat jejunal mucosa by Kowarski et al and which is apparently involved in active transport of zinc across the intestinal mucosa.
Hypogonadal Dwarfism

The syndrome of zinc-deficient hypogonadal dwarfism was first reported in 1963 by Prasad and his associates and has been studied extensively by these workers. The subjects in these studies have been adolescent males with dwarfism, retardation of sexual maturation, iron-deficiency anemia and hepatosplenomegaly, who live in rural Iran and Egypt. The laboratory and clinical evidence of zinc-deficiency in these subjects has included: (1) low concentrations of zinc in plasma, erythrocytes and hair; (2) low excretions of zinc in urine and sweat; (3) increased turnover of $^{65}$Zn in plasma; (4) low cumulative excretions of $^{65}$Zn in urine and feces; and (5) skeletal growth and gonadal development after dietary zinc supplementation. Zinc deficiency in these subjects apparently is the result of interference with zinc absorption owing to the large amount of phytate which is present in the native diet. Ronaghy and coworkers have reported a thorough two-year study of zinc supplementation in malnourished Iranian school-boys in which they have been confirmed that oral ZnSO$_4$ provides an unequivocal stimulus to skeletal growth. Caggiano et al in New York have reported a 21-year-old Puerto Rican man with dwarfism, hypogonadism and zinc deficiency. Within three months after zinc supplementation was instituted, this man's height increased by seven cm; his genitalia became significantly larger; and he developed secondary sexual characteristics. Sandstead et al in Tennessee have described a 20-year-old man with regional enteritis, growth failure and hypogonadism who responded to oral zinc supplementation. On the basis of these several reports, zinc deficiency can be regarded a pathogenetic factor in certain cases of human hypogonadal dwarfism.

Congenital Malformations

Maternal zinc deficiency may play a role in the pathogenesis of congenital anomalies in man. This hypothesis has arisen on the basis of findings by Hurley and coworkers that short-term depletion of zinc in maternal rats results in a wide variety of congenital anomalies in the offspring. Warkany and Petering have furnished independent confirmation of these observations. For example, administration of a zinc-deficient diet to pregnant rats for only six days (i.e. from the 7th to 12th days of gestation) produced nine percent incidence of congenital anomalies, including hydrocephalus, exencephalus, cleft lip and palate, as well as ocular and skeletal malformations. The homeostatic regulation of plasma zinc concentration is dependent upon constant availability of dietary zinc, and pregnant rats are apparently unable to mobilize zinc from body stores for the benefit of their fetuses. Thus, Dreosti et al have shown that administration of a zinc-deficient diet to pregnant rats for only one day produced a 38 percent reduction in plasma zinc concentration. Swenerton et al have reported that uptake of $^3$H-thymidine into DNA is reduced in 12-day embryos of rats which ingested zinc-deficient diets. Based upon this observation and the recent discovery that DNA-polymerase is a Zn-metalloprotein, Hurley and Shrader have proposed that impaired DNA synthesis in zinc-deprived embryos prolongs the mitotic cycle and reduces the number of neural tube cells, leading to malformations of the central nervous system. Sever and Emanuel have suggested that the exceptionally high rates of human malformations of the central nervous system in Alexandria, Egypt and Shiraz, Iran might be caused by maternal zinc deficiency. Henkin has studied human maternal-fetal interrelationships of zinc by measuring zinc concentrations in maternal
serum, umbilical cord serum and amniotic fluid obtained after uncomplicated pregnancies with normal deliveries at term. He found that the mean concentration of zinc in maternal serums (48 µg per dl, S.E. ± 3) was significantly less than that in umbilical cord serums (83 µg per dl, S.E. ± 3). The zinc concentration in amniotic fluid averaged 32 µg per dl, S.E. ± 12. Insofar as the author can ascertain, comparable measurements have not been performed in instances of congenital malformations.

**Hypogeusia and Hyposmia**

An association between trace metal deficiency and hypogeusia (diminished taste sensation) was first reported in 1967 by Henkin et al. These investigators found hypogeusia in 23 (32 percent) of a group of 73 patients with rheumatoid arthritis, scleroderma, cystinuria or idiopathic pulmonary fibrosis who were being treated with D-penicillamine. D-penicillamine treatment in these subjects produced copper deficiency, as evidenced by diminished concentrations of serum copper and ceruloplasmin. In contrast, hypogeusia was found in only four of 100 patients with Wilson's disease who were receiving D-penicillamine treatment for copper overload. Henkin et al reasoned that copper depletion might be responsible for the greater incidence of hypogeusia in the first group of patients. In support of this hypothesis, they found that oral administration of Cu(II) to four of these patients resulted in improvement of hypogeusia, even though D-penicillamine treatment was continued without interruption. Henkin and Bradley subsequently reported that oral administration of either Ni(II), Zn(II), or Cu(II) improved taste acuity in patients with hypogeusia. Hambidge et al observed five children in whom hypogeusia was associated with poor growth, anorexia and low concentrations of zinc in hair. After dietary supplementation with ZnSO₄, taste acuity was normalized in each of these children, and the concentrations of zinc in hair increased. Schecter and coworkers reported a trial of oral ZnSO₄ therapy in adult patients with idiopathic hypogeusia. In two-thirds of these patients, hypogeusia began during or after an illness such as an acute upper respiratory infection, while in the remaining one-third of these patients, hypogeusia did not follow any apparent malady. In most of these subjects, hypogeusia was associated with hyposmia (diminished olfactory sensation). In this study, improved taste acuity occurred in 12 (67 percent) of 18 patients who were treated with oral ZnSO₄ in dosage of 100 mg per day. In comparison, improved taste acuity was experienced by only four (22 percent) of 18 patients while they were receiving a placebo. Additional evidence of an association between hypogeusia and altered zinc metabolism has been reported by Cohen et al in patients with thermal burns. Hypogeusia was detected in 16 of 19 patients with severe burns. In the burned patients with hypogeusia, the mean concentration of serum zinc was decreased and the mean excretion of zinc in urine was increased. Henkin and Smith have noted that hypogeusia and hyposmia frequently develop in patients with acute viral hepatitis, a condition which is commonly associated with hypozincemia. The various studies which have been cited suggest that deficiencies of zinc and other trace metals are involved in the pathogenesis of hypogeusia and hyposmia, but the pathogenetic mechanisms remain obscure. Culliton has reported on the current controversy in this matter.

**Nyctalopia**

A possible relationship between zinc deficiency and nyctalopia (night blindness) has arisen from the recent discovery that zinc influences the metabolism of retinol (vitamin A alcohol). Saraswat and
<table>
<thead>
<tr>
<th>Investigators</th>
<th>Date</th>
<th>Lesions</th>
<th>No. of Patients</th>
<th>Observation on Reepithelialization Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pories et al</td>
<td>1966</td>
<td>Pilonidal sinus</td>
<td>10</td>
<td>2-fold increase vs controls</td>
</tr>
<tr>
<td>Cohen</td>
<td>1968</td>
<td>Bedsores</td>
<td>0</td>
<td>Improvement</td>
</tr>
<tr>
<td>Husain</td>
<td>1969</td>
<td>Leg ulcers</td>
<td>52†</td>
<td>&gt;2-fold increase vs controls</td>
</tr>
<tr>
<td>Barcia</td>
<td>1970</td>
<td>Pilonidal sinus</td>
<td>10</td>
<td>No influence vs controls</td>
</tr>
<tr>
<td>Greaves &amp; Skillen</td>
<td>1970</td>
<td>Leg ulcers</td>
<td>0</td>
<td>Complete healing in 11; partial healing in 7</td>
</tr>
<tr>
<td>Serjeant et al</td>
<td>1970</td>
<td>Leg ulcers</td>
<td>17</td>
<td>3-fold increase vs controls</td>
</tr>
<tr>
<td>Myers &amp; Cherry</td>
<td>1970</td>
<td>Leg ulcers</td>
<td>16</td>
<td>No influence vs controls</td>
</tr>
<tr>
<td>Clayton</td>
<td>1972</td>
<td>Leg ulcers</td>
<td>5</td>
<td>Slower in treated vs controls</td>
</tr>
<tr>
<td>Greaves &amp; Ives</td>
<td>1972</td>
<td>Leg ulcers</td>
<td>18</td>
<td>No influence vs controls</td>
</tr>
<tr>
<td>Hallbøk &amp; Lanner</td>
<td>1972</td>
<td>Leg ulcers</td>
<td>14</td>
<td>4-fold increase vs controls in pts. with low serum Zn; no influence vs controls in pts. with normal serum Zn</td>
</tr>
</tbody>
</table>

*ZnSO₄, 220 mg t.i.d. †Double-blind study

Arora have found that concentrations of serum retinol are lower in zinc-deficient lambs than in zinc-supplemented controls. Smith et al have reported that zinc is necessary for the mobilization of retinol from the liver, and they have observed that zinc-deficient rats are unable to maintain normal plasma concentrations of retinol. Moreover, Smith and coworkers have observed that zinc-deficient rats have diminished concentrations of serum retinol-binding protein, a low molecular weight α-globulin. Smith and coworkers have found correlation between diminished serum concentrations of zinc and retinol in children who reside in a ghetto locality in Baltimore. Henkin and Smith have reported correlation between diminished concentrations of plasma zinc and plasma retinol-binding protein in patients with viral hepatitis. On the basis of these findings, Henkin and Smith have suggested that alterations of zinc metabolism may influence the concentration of plasma retinol-binding protein. Halsted and Smith have speculated that there also may be a zinc requirement for the conversion of retinol (vitamin A alcohol) to retinal (vitamin A aldehyde) by retinene reductase in the retina. There is obviously a need for controlled clinical trials of zinc supplementation in patients (e.g. chronic liver disease) who have impaired visual adaptation to darkness, and especially in those patients who are unresponsive to vitamin A supplementation.

Impaired Wound Healing

In 1966, Pories and collaborators reported that oral administration of ZnSO₄ to military personnel with marsupialized pilonidal sinuses was attended by a two-fold increase in the rate of reepithelialization. The authors' conclusion that ZnSO₄ can promote the healing of cutaneous sores and wounds has been a subject of controversy during the ensuing seven years. As summarized in table I, clinical investiga-
tions by Cohen,19 Husain,73 Greaves and Skillen,45 and Serjeant et al142 have substantiated the beneficial effects of ZnSO₄ on wound healing, whereas studies by Barcia,5 Myers and Cherry,101 Clayton,78 and Greaves and IVe44 have failed to demonstrate any therapeutic benefit. Hallböök and Lanner48 found that the reepithelialization rate of venous leg ulcers was enhanced by ZnSO₄ in patients who initially had diminished concentrations of serum zinc, but they did not find any benefit in patients whose initial measurements of serum zinc were within the normal range. On the other hand, Husain et al74 did not observe any relationship between response to zinc treatment of venous leg ulcers and the initial measurements of plasma zinc. Flynn et al35,36 reported profound hypozincemia and delayed wound healing in patients who received long-term corticosteroid therapy following bilateral adrenalectomy and in patients who received corticosteroids for treatment of collagen disorders. Wound healing was enhanced in these subjects following oral zinc supplementation. Carruthers16 and Henkin59 have independently reviewed the conflicting clinical evidence, and have concluded that administration of ZnSO₄ to patients who are zinc-deficient is one of the factors which accelerates the healing of cutaneous wounds. This conclusion is supported by studies in experimental animals which have demonstrated that: (1) healing of incised wounds is impaired in rats with dietary zinc deficiency;102,129,135 (2) synthesis of desoxyribonucleic acid (DNA), ribonucleic acid (RNA), collagen and non-collagen proteins is reduced in skin and connective tissues from rats with dietary zinc deficiency;34,92,149 (3) zinc supplementation does not augment wound healing in normal rats;46,68 and (4) zinc supplementation does augment wound healing in chronically ill rats.31 If a clinician accepts the conclusion that zinc supplementation promotes wound healing in zinc-deficient patients, the clinician is then confronted with the difficult question of how to diagnose zinc deficiency. As Henkin59 has emphasized, there is no ready answer to this question, owing to the complex interactions of pathophysiological mechanisms which influence zinc metabolism.

Pathophysiological Mechanisms of Hypozincemia

The various pathophysiological mechanisms which have been implicated in the production of hypozincemia include: (1) nutritional deficiency and/or intestinal malabsorption of zinc;12,15,90,125,135 (2) increased urinary excretion of zinc secondary to aminoaciduria (e.g. histidine and cysteine), frequently associated with tissue catabolism;33,41,42,56,124 (3) zinc losses in sweat during profuse perspiration;32,66,128,158 (4) diminution of serum zinc secondary to hypoalbuminemia;11,68 (5) alteration of body zinc pools and increased urinary excretion of zinc secondary to adrenal release of cortisol and pituitary release of growth hormone (e.g. following stress);28,47,57,58,63 (6) alteration of body zinc pools produced by endogenous estrogens (e.g. pregnancy) or exogenous estrogens (e.g. oral contraceptives);13,50,76,134 and (7) alteration of body zinc pools produced by “leukocytic endogenous mediator” (LEM).8,78,104,105,109 LEM is a heat-labile protein released from sensitized polymorphonuclear leukocytes, which produces prompt hypozincemia with concomitant increase in hepatic zinc.109 LEM is apparently involved in many facets of the “acute phase reaction,”70,78,79,108 and there is evidence that LEM may be responsible for the hypozincemia which occurs during acute infections and inflammatory conditions.10,119 The hypozincemia which is produced by LEM, as well as that which is seen in uremia,119 is mediated by redistribution of zinc within body pools, without zinc deficiency neces-
 Conditions Associated with Hypozincemia

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>52, 54, 88, 89, 156</td>
</tr>
<tr>
<td>Acute infections</td>
<td>9, 10, 52, 89, 107</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>66</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>11, 49, 52, 126, 139, 155, 157</td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>7, 25, 91</td>
</tr>
<tr>
<td>Leukemias and lymphomas</td>
<td>2, 134</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>134, 161</td>
</tr>
<tr>
<td>Chronic uremia</td>
<td>21, 52, 93, 160, 161</td>
</tr>
<tr>
<td>Malabsorption states</td>
<td>90, 157</td>
</tr>
<tr>
<td>Kwashiorkor</td>
<td>137</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>162</td>
</tr>
<tr>
<td>Mongolism</td>
<td>52, 95</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>93</td>
</tr>
<tr>
<td>Surgical stress</td>
<td>33, 85, 88, 141</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>57</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>58</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>50, 76, 134</td>
</tr>
<tr>
<td>Chronic debilitation (e.g. paraplegia, cystic fibrosis)</td>
<td>52</td>
</tr>
<tr>
<td>Drugs (estrogens, oral contraceptives)</td>
<td>13, 50, 35, 36, 62</td>
</tr>
</tbody>
</table>

sarily being present. Therefore, reliance cannot be placed solely upon measurements of plasma zinc for the diagnosis of zinc deficiency.

A tabulation of clinical conditions which are associated with hypozincemia is presented in table II. The several pathophysiological mechanisms which have been mentioned may function to varying degrees in these several disorders. In order to assess zinc nutriture in patients, it is frequently desirable to measure zinc in diverse biological samples, including urine, blood cells, hair, sweat, saliva and amniotic fluid. Studies with caution for diagnostic purposes, owing to the long residence time of $^{65}$Zn in the human body and the presence of zinc in DNA polymerase and reverse transcriptase. As additional approaches to assessment of zinc nutriture, measurements of zinc in plasma ultrafiltrates of $^{65}$Zn are invaluable for clinical research, but should be approached and spinal fluid may be attempted. Consideration may also be given to measurements of urinary excretion of zinc before and after infusion of chelating agents such as calcium-EDTA (edathamil) or DTPA (diethylenetriaminepentaacetic acid). Finally, in many cases it is desirable to perform a therapeutic trial of oral supplementation with ZnSO$_4$.

**Difficulties in Measurements of Zinc in Plasma and Other Biological Materials**

Methods for zinc analysis in body fluids and excreta are beyond the scope of this discussion, and have been thoroughly considered in several recent articles. However, it is germane to emphasize that errors in sampling and analysis frequently contribute to the difficulties of clinical evaluation of zinc metabolism. As Versieck et al and Ronaghy et al have reported, specimen collection and analytical performance are often inadequate, and zinc contamination is rampant. As a consequence, grossly inaccurate measurements of zinc in plasma and other biological samples are encountered. In the present author's experience, the following procedures are essential in order to achieve valid analytical results:

**Fasting patient under basal conditions.** Blood should be collected between 6 and 8 A.M., while the patient remains in bed after a 15 hour overnight fast. This precaution is necessary in order to avoid fluc-
TABLE III
Circadian Variations of Zinc Concentrations in Serum or Plasma

<table>
<thead>
<tr>
<th>Authors</th>
<th>Date</th>
<th>No. of Subjects</th>
<th>Specimen*</th>
<th>Zinc Concentrations at Specified Times</th>
<th>Units and Statistical Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hellwege55</td>
<td>1970</td>
<td>15#</td>
<td>S</td>
<td>8 A.M. 129(85-170) 12 Noon 111(75-165) 6 P.M. 100(65-120)</td>
<td>ug/dl; mean (range)</td>
</tr>
<tr>
<td>Lifschitz &amp; Henkin87</td>
<td>1971</td>
<td>10</td>
<td>S</td>
<td>6 A.M. -8 ± 2.5 2 P.M. +2.5 ± 2.5 10 P.M. +7 ± 2.5</td>
<td>% change; mean ± S.E.</td>
</tr>
<tr>
<td>Hetland &amp; Brubakk67</td>
<td>1973</td>
<td>13</td>
<td>S</td>
<td>8 A.M. 104 ± 12 11:30 A.M. 96 ± 8 5 P.M. 93 ± 9</td>
<td>ug/dl; mean ± S.D.</td>
</tr>
<tr>
<td>Burr14</td>
<td>1973</td>
<td>9</td>
<td>P</td>
<td>7 A.M. 115 ± 3 12 Noon 101 ± 3 6 P.M. 89 ± 3</td>
<td>ug/dl; mean ± S.E.</td>
</tr>
<tr>
<td>Walker et al157</td>
<td>1973</td>
<td>20</td>
<td>P</td>
<td>9 A.M. 97(80-130) 1 P.M. 81(65-90)</td>
<td>ug/dl; mean (range)</td>
</tr>
</tbody>
</table>

*S. = serum, P = plasma #Children †Percent deviation from each subject’s 24 hour mean

Circadian variations in plasma zinc concentrations owing to the effects of exercise, food and circadian rhythms.11 In table III are given illustrative results from investigations in which zinc analyses were performed upon serum or plasma samples obtained from healthy subjects at various times of the day. Circadian variations of zinc concentrations were found in all of these studies. In four of these five investigations, the mean concentrations of zinc were found to be significantly higher in the early morning specimens than in specimens which were obtained at other times.

Acid-washed glassware. All glassware which is used for specimen collection, processing and analysis should be washed with nitric acid and rinsed with copious distilled-deionized water. Acid-washing is particularly important for syringes, blood-collection tubes, Pasteur pipets and plastic test-tubes. It may be noted that “lead-free” Vacutainer tubes* are not acid-washed by the manufacturer, and they are frequently contaminated with zinc.

Analysis of plasma rather than serum. It is preferable to analyze plasma rather than serum, since the concentration of zinc in serum averages 16 percent higher than in plasma, owing in part to platelet release of zinc during clotting.87 Each batch of heparin solution which is used as an anticoagulant should be tested to ensure that it is not contaminated with zinc. Hemolysis should be scrupulously avoided in measurements of plasma zinc, since erythrocytes are rich in zinc-containing metalloproteins (e.g. carbonic anhydrase).

Analytical quality control. Many laboratories neglect to perform routine measurements of zinc in samples of pooled plasma and urine in order to monitor day-to-day variations in analytical results. Quality control specimens should always be included with each batch of analyses. In addition, it is desirable to perform frequent measurements of the recovery of zinc added to plasma, urine and other materials, and to participate in inter-laboratory comparisons of zinc in “unknown” samples.

Conclusions

On the basis of the clinical and experimental studies which have been discussed, there is evidence that zinc deficiency may play an important role in the pathogenesis of (1) acrodermatitis enteropathica, and in
certain cases of (2) hypogonadal dwarfism, (3) congenital malformations, (4) hypogeousia and hyposmia, (5) nictalopia and (6) impaired wound healing. Pfeiffer and Iliev\textsuperscript{115} have speculated on tenuous grounds that zinc deficiency may also be involved in schizophrenia, and Barbeau and Donaldson\textsuperscript{4} have proposed a relationship between zinc deficiency and epilepsy. The clinical diagnosis of zinc deficiency is complicated by complex interactions of several pathophysiological factors which induce hypozincemia in a wide variety of pathological conditions. Diagnosis of zinc deficiency is further complicated by practical problems in sampling and analysis of zinc in body fluids and excreta. A serious need exists for improved laboratory techniques for the diagnosis of zinc deficiency in man.

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