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Zinc and the Special Senses

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There is evidence that zinc is important for maintenance of the special senses: vision, taste, and smell. Rod function is impaired in zinc deficiency due partly to its role in vitamin A metabolism. However, optic nerve function may also be affected by zinc status. Microophthalmia, anophthalmia, and optic nerve abnormalities have all been found in the offspring of female rats fed zinc-deficient diets. Zinc deficiency clearly decreases taste acuity in both animals and humans. However, other nutritional and non-nutritional conditions also produce hypogeusia. There is limited evidence that zinc deficiency impairs olfactory acuity in humans. New approaches to the assessment of taste and smell abnormalities may provide reliable and reproducible associations between zinc deficiency and taste and smell defects.

RECENT EVIDENCE shows that zinc is essential for the maintenance of vision and taste. Zinc's role in maintaining normal rod function may be a result of its metabolic interaction with vitamin A (1). Cone and optic nerve function may also be affected by zinc, and zinc deficiency has been implicated as a cause of congenital fetal abnormalities involving the eye.

One of the striking consequences of zinc deficiency in experimental animals is growth retardation. The spontaneous intake of zinc-depleted animals is markedly reduced (2, 3). Thus, decreased appetite was early recognized as a manifestation of zinc deficiency. In 1963, a form of nutritional zinc deficiency in humans was reported among rural villagers in remote regions of Egypt; geophagia (pica) was a characteristic of that syndrome (4). Whether the habit was culturally or physiologically based, and whether it was practiced to a greater extent by the zinc-deficient villagers as compared with their better nourished peers cannot be established with certainty from these early reports. In any event, a suspicion that zinc deficiency affected taste perception and gustatory function emerged from early observations on zinc deficiency in experimental animals, domestic livestock, and human populations. Studies in laboratory animals, analyses of saliva and oral tissues, clinical observations, and zinc supplementation and depletion trials in humans helped to clarify the issue of zinc deficiency and gustatory and smell function. No clear picture has yet emerged, but some tentative conclusions and associations can be derived from a substantial body of accumulated data. We discuss the relevant information available on the role of zinc in vision, taste, and smell.

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Vision

ABSORPTION AND METABOLISM OF ZINC AND VITAMIN A

The main source of zinc in the American diet is meat (5). A diet containing 1 g of protein per kg of body weight for a 70-kg human contains approximately 12.5 mg of zinc. Normally, only a small percentage is absorbed, and the mechanism of absorption remains poorly understood. One postulate is that zinc is taken up by the microvilli of the mucosal cells of the small intestine, although it is uncertain which area of the small bowel is most important for absorption (6, 7). Inside the cell, zinc attaches to several different ligands, one of which transports zinc to the serosal side of the cell where it emerges to be coupled to a circulating transport protein (8). In the rat, prostaglandin E_2 has been found in intestinal cytoplasmic extracts and appears to augment zinc absorption and transport (9). Indomethacin, a prostaglandin inhibitor, inhibits zinc absorption in rats. Zinc is excreted nearly totally through the gut. With zinc intakes ranging from 14.0 to 15.1 mg/d, average fecal zinc excretion in humans was 11.8 to 13.7 mg/d. Urinary output ranged from 0.6 to 0.8 mg/d (10). It has been estimated that the amount of dietary zinc needed to be absorbed daily by the healthy adult is 2.5 to 4.0 mg/d (11). Therefore, fecal zinc contains unabsorbed zinc and zinc that is secreted from the vascular space into the intestine. A number of dietary factors (phytate, fiber) and malabsorption syndromes (gluten enteropathy, short bowel, cystic fibrosis, Crohn's disease) interfere with the normal absorption of dietary zinc (12). Once in the blood, zinc is delivered to its target tissues and is involved in more than 70 metalloenzymes (13). In alcoholic cirrhosis, renal zinc excretion is increased apparently as a consequence of binding with low-molecular-weight amino acids, which are subsequently filtered out by the renal glomerulus and not reabsorbed (14-16). In addition, zinc wastage also occurs in sickle cell disease and other chronic hemolytic anemias (17).

Vitamin A and carotenoids are provided in the diet. In the stomach and small intestinal lumen, these compounds are liberated into fatty globules, dispersed by bile salts, hydrolyzed, incorporated into mixed micelles, and eventually absorbed by the intestinal mucosal cells. Dietary protein, fat, and bile enhance the digestion and absorption of vitamin A esters and carotenoids (18-22). In rats, zinc deficiency may impair the conversion of carotene to retinol through reduced retinal reductase activity (23). Some vitamin A is transported through the portal circulation with low-density lipoproteins, but the vast majority

is transported as vitamin A ester with the low density lipoproteins of lymph. At the liver cell membrane, vitamin A esters are hydrolyzed by an esterase enzyme, liberating the alcohol form of vitamin A, retinol (24). For storage in the liver, retinol must be converted back to its ester form, to remain as a soluble lipoprotein aggregate until peripheral use of vitamin A requires its release (HELLER J Personal communication).

To be released in the blood, vitamin A esters must be hydrolyzed back to retinol, which then binds in a one-to-one molecular relation to available retinol binding protein within the liver cell (25-27). Adequate protein is needed for hepatic synthesis of retinol binding protein. Once released into circulation, this retinol-retinol binding protein package is joined with one molecule of prealbumin, which is the form in which vitamin A circulates.

Numerous important metabolic interactions of zinc and vitamin A have been documented in two recent reviews (1, 28). Some of this information is germane to the understanding of the role of zinc in vision.

ROD FUNCTION

Vitamin A is essential to the maintenance of retinal rod function and dark adaptation. Vitamin A deficiency is a worldwide health problem and one of the most frequent causes of preventable blindness today. It is estimated that 500 000 Asian children worldwide go blind every year from vitamin A deficiency (29). Early and mild vitamin A deficiency leads to a measurable decrease in dark adaptation, but more severe and prolonged deficiencies can cause retinal morphologic changes, xeropthalmia, corneal ulceration and perforation, and permanent blindness. In recent years, an interaction between zinc and vitamin A has been elucidated, and both micronutrients appear to be necessary for maintenance of normal rod function.

Retinal pigment epithelial cells have specific receptors for retinol binding protein that permit the entry of retinol into these cells and, eventually, into the photoreceptor cells (that is, rod and cones) of the retina (30, 31). It is noteworthy that electron opaque inclusions have been found in the retinal pigment epithelial cells of rats treated with intraperitoneal injections of specific zinc chelators (32). However, the biochemical composition and functional significance of such inclusions are uncertain. During the transfer of vitamin A to photoreceptor cells, retinol is enzymatically converted to vitamin A aldehyde (retinal) Retinal, when joined with opsin in the rods, forms the visual pigment rhodopsin (33, 34). Illumination of the retina bleaches rhodopsin, causing a release of all transretinaldehyde—some of which is reduced back to retinol, and some of which is lost. Retinol dehydrogenase is needed for the interconversion of retinol and retinaldehyde (35). This substance is not the same alcohol dehydrogenase that is present in the liver and responsible for the conversion of ethanol to acetaldehyde. However, zinc may be an integral component of retinol dehydrogenase and may be needed for proper enzyme function (36).

Huber and Gershoff (36), in an effort to determine the effects of zinc deficiency on retinol dehydrogenase, produced zinc deficiency in adult and weanling rats The zinc content of the eye was lower in zinc-deficient animals than in controls given zinc-sufficient diets and as much food as desired. The rate of conversion to the respective aldehyde per milligram of tissue was also significantly reduced in the zinc-deficient adults and pups when either retinol or ethanol was used as substrate. Unfortunately, zinc levels of pair-fed controls were not tested.

The first indication in humans that factors other than vitamin A were important in dark adaptation was found in 1939 by Patek and Haig (37) who reported that 19 of 24 patients with cirrhosis had abnormal dark adaptation despite diets adequate in vitamin A intake. Even with massive doses of vitamin A, certain patients remained night blind. In 1959, Vallee and associates (38) speculated that altered zinc metabolism was responsible for the poor dark adaptation responses of some cirrhotic patients. Subsequently, Morrison and colleagues (39) found that the dark adaption of six alcoholic patients with cirrhosis who had a zinc deficiency became normal with zinc therapy. Two of the five responders were first treated with vitamin A and did not correct their dark adaptation defect. Subsequently, wih zinc sulfate, 220 mg/d taken orally, both patients normalized their dark-adapted final threshold in 1 to 2 weeks. In the two patients who responded to zinc, serum retinol binding protein levels were measured during therapy (40); both had low retinol binding protein levels at the onset with no change in levels accompanying zinc therapy. Thus, in these patients, zinc probably either increased the activity of retinol dehydrogenase of the retina resulting in the regeneration of retinaldehyde or acted in the retinal nerve cells. Supportive data are offered by other observations (41, 42). McClain and coworkers (41) supplemented with zinc the diets of six zinc-deficient, alcoholic, cirrhotic patients with abnormal dark adaptation and found a return of normal night vision. Warth and associates (42) gave zinc to three patients with sickle cell disease and low neutrophil zinc levels and showed subsequent improvement in dark adaptation; unfortunately, retinol binding protein levels after zinc therapy were not provided. Toskes and colleagues (43-45) have described an interesting group of patients with chronic pancreatitis and abnormal dark adaptation associated with equatorial punctate lesions of the retina. Although abnormal retinal function did not correlate with serum vitamin A or zinc levels, treatment with vitamin A and zinc resulted in improvement in the final dark-adapted threshold.

Using bovine retinas, Tam and coworkers (46) showed the presence of appreciable amounts of zinc in isolated rod outer segments and emulphogene extracts of rod outer segments. Further, the zinc content of the protein fractions derived from emulphogene extracts of rod outer segments were found to be stoichiometrically related to rhodopsin. Light treatment increased the zinc content of the protein fraction by 60% over the zinc content of protein fractions from dark-adapted retinas. The authors concluded that zinc may play a role in the photoisomerization of rhodopsin in rods.

Zinc and vitamin A interactions in the liver may also be important for the maintenance of normal plasma vitamin A levels, and, hence, for normal night vision. Although these interactions have been the subject of much investigation, the actual role of zinc in vitamin A mobilization remains controversial. The controversy focuses on the question of whether zinc deficiency specifically affects the synthesis or mobilization from the liver of retinol-binding protein or whether zinc deficiency results nonspecifically in decreased protein intake and synthesis, thus reducing levels of retinol-binding protein.

In 1973, Smith and associates (47), studying zinc deficient rats, found a 50% reduction in plasma vitamin A concentrations but normal liver stores of vitamin A. When zinc, but not vitamin A, normalized plasma vitamin A levels, the investigators postulated that the zinc-deficient rats were unable to mobilize vitamin A from the liver due to impaired synthesis or release of retinol-binding protein. To study the effects of decreased food intake and growth retardation on retinol-binding protein and vitamin A levels, Smith and colleagues (48) compared three groups of animals: those fed a zinc-deficient diet; those pair-fed a zinc-sufficient diet; and those allowed to eat as much as desired. The pair-fed rats with normal zinc intake were found to have retinol-binding protein and vitamin A levels intermediate between those in zinc-deficient rats and those in the controls allowed to feed freely. Liver retinol-binding protein concentrations were decreased by one half in the zinc-deficient group versus both the control groups. This study suggests that zinc deficiency depressed retinol-binding protein synthesis in the liver. However, because total plasma proteins were also decreased in the zinc-deficient group, the effect does not appear to be entirely specific for retinol-binding protein, but rather a more generalized effect on protein synthesis.

Ette and coworkers (49) gave intraperitoneal zinc to normal weanling rats and showed that, 2 hours after administration, plasma vitamin A increased and liver vitamin A decreased. These data support a role for zinc in the mobilization of vitamin A from the liver. Unfortunately, retinol-binding protein was not measured, so the mechanism of increased plasma vitamin A in this study remains uncertain. It must also be noted that, in this study, zinc was given in a very large dose (10 mg) and in an unnatural way. Carney and associates (50), however, have shown that zinc deficiency is not a limiting factor in hepatic vitamin A release except as it influences growth and body demand for vitamin A. When weanling rats with zinc deficiency or zinc and vitamin A deficiency were given tritiated vitamin A, there was no defect in the ability of the animals to mobilize newly ingested vitamin A. Tao and Hurley (51) have shown quite the opposite: zinc deficient rats were found to have lower protein levels than either pair-fed or pair-weighed controls. These results support a role for zinc in protein synthesis and metabolism, which cannot be explained by inanition.

The best data suggesting a direct role for zinc in vitamin A metabolism in the liver of humans come from India where children with protein-energy malnutrition and zinc deficiency were maintained on their protein-deficient diets but given zinc supplements (52). This treatment resulted in significant increases in vitamin A and retinol-binding protein levels in the plasma. In Jamaica, Mathias (53) found elevated levels of vitamin A and retinol-binding protein whether or not zinc supplementation was given to children being treated for protein-calorie malnutrition. However, the high vitamin A levels were sustained only in the zinc-supplemented group.

CONE FUNCTION AND OPTIC NEUROPATHY

The association of zinc and cone function has not been well studied. However, a few reports have implied a role for zinc in color vision, central macular vision, and optic nerve integrity.

Weismann and colleagues (54) found 4 of 23 cirrhotic men to have red/green color blindness. As a group, these patients had low plasma zinc levels, but individual levels were not given. Zinc supplementation had no effect on color vision in these patients, indicating that zinc was not important in causing these abnormalities. However, blue/yellow color blindness has been shown to be increased among alcoholic patients with cirrhosis, and acute alcohol ingestion by alcoholic or normal persons can result in blue/yellow color blindness (55). Zinc deficiency has not been implicated in this abnormality, but has a potential role because both the prevalence of blue/yellow color blindness and zinc deficiency among alcoholic and alcoholic and cirrhotic patients are high.

Among patients with chronic pancreatitis described by Toskes and coworkers (45) abnormal B type waves on electroretinography in light adaptation (a measure of cone function) and abnormal findings of electro-oculograms were found for several patients who had low serum zinc levels (45). Klingberg and associates (56) reported a patient with Wilson's disease who, during treatment with penicillamine, developed an irreversable diminution of visual acuity and a centrocecal scotoma. Because the patient had low erythrocyte and plasma zinc levels at the time of the vision changes, the problem was ascribed to zinc deficiency from chelation of zinc by penicillamine.

Yassur and colleagues (57) recently reported that a 23-year-old patient with Crohn's disease developed bilateral maculopathy—manifested by decreased visual acuity and visual field restriction—after a 3-week course of total parenteral nutrition. The electroretinogram was normal. The serum levels of zinc and copper were depressed (30 μg/dL and 70 μg/dL, respectively), and the serum alkaline phosphatase was 35 IU/L (normal, 45 to 85 IU/L). Two weeks after zinc and copper were administered and parenteral nutrition was discontinued, no signs of maculopathy were found and visual fields were normal, the measurements of serum zinc, copper, and alkaline phosphatase were normal.

Other evidence that zinc deficiency may result in cone dysfunction comes from studies in patients with acrodermatitis enteropathica. Acrodermatitis enteropathica is a rare autosomal recessive disorder of zinc deficiency resulting from defective intestinal absorption of the metal

(58). Clinical signs and symptoms include alopecia, rash, and diarrhea identical to those seen in kwashiorkor and hyperalimentation-induced zinc deficiency. Ocular findings include photophobia, gaze aversion, corneal opacities, blepharitis, conjunctivitis, stenosis of the puncta, and cataracts (59, 60). All of these signs and symptoms may be secondary to zinc deficiency. The most striking ocular manifestation of acrodermatitis enteropathica is gaze aversion, the avoidance of eye-to-eye contact. This may indicate that the patient finds central cone vision distressing and will rely on peripheral vision, which is rod dependent (61).

From 1953 to 1971, the therapy for acrodermatitis enteropathica consisted of continuous high doses of 5,7-dihalo-8-quinolinols (principally diiodohydoxyquin, but also iodochlorohydroxyquin). Both of these drugs are known to chelate zinc but the actual mechanism of these drugs in treating acrodermatitis enteropathica remains unknown. Michaelsson (62) reported a case of impaired color vision in a patient with acrodermatitis enteropathica who had been taking chloroquinadol for years. After stopping treatment with this drug and starting zinc therapy, color vision returned to normal. The exact nature of the color vision abnormality was not defined. Leopold (63) interpreted this case as possibly showing a sensitivity of cones to zinc, but whether the color vision deficit was secondary to zinc deficiency or the toxic effect of chloroquinadol remains uncertain.

The occurrence of at least six cases of optic atrophy and neuropathy in patients with acrodermatitis enteropathica has increased the speculation that zinc deficiency may be responsible for this eye lesion (64). Zinc has been shown to be necessary for the stablization of microtubules in rat brain homogenates (65). Microtubules seem to play a role in rapid axonal transport, and in vitro, rapid axonal transport in frog nerve cells is markedly influenced by the zinc concentration of the incubation fluid (66). Since 1973, zinc has been the primary therapy for acrodermatitis enteropathica and there have been no additional reports of optic atrophy occurring. Weismann and coworkers (67) reported a striking case history relating zinc deficiency to optic atrophy (67). A 51-year-old woman lived mainly on beer and had had a Bilroth II gastric resection. She developed hypozincemia and a clinical syndrome similar to acrodermatitis enteropathica (that is, diarrhea, rash, alopecia, and mental impairment). She also had decreased visual function of both eyes with bilateral optic atrophy. This syndrome developed in the absence of dihaloquinolinols and provides circumstantial evidence for the direct role of zinc deficiency in causing optic atrophy in patients with acrodermatitis enteropathica.

Zinc may also have a role in the pathogenesis of certain other toxic optic neuropathies (63). Ethambutol is known to cause optic neuritis. The in-vivo chelating action of the drug for zinc may be responsible for this lesion by limiting the availability of zinc to the eye. Serum zinc levels were found to be low in three cases of optic neuritis induced by ethambutol, one by disulfiram and seven by alcohol and tobacco intoxication (68). These patients had similar clinical presentations with onset usually heralded by dyschromatopsia of the red/green color axis. The neuritis is usually retrobulbar in the early stages. Although this correlation of optic neuritis with low serum zinc levels does not prove that zinc is responsible for optic neuritis, it is interesting that many drugs that chelate zinc show are toxic to the optic nerve.

CONGENITAL VISUAL IMPAIRMENT

The importance of zinc in prenatal development is well documented. Hurley and associates (69) have shown that newly mated female rats fed severely zinc deficient diets from days 0 to 21 of pregnancy had 41% embryo reabsorption and 90% to 100% of the live offspring had malformations (42% with microophthalmia or anophthalmia). In a similar previous study by Hurley and colleagues (70), 32% of offspring of zinc deficient mothers had small or missing eyes. Shorter periods of zinc deficiency were also teratogenic. When the mother rats were transferred to a zinc-supplemented diet as late as day 10, the incidence of eye abnormalities was reduced; if zinc supplementation was begun before day 10, the eye abnormalities were almost completely prevented. Low-zinc diets started later in gestation (after day 8) produced no ocular abnormalities. These data suggest that the eye, which develops early in gestation, is affected by early but not late decreases in zinc intake. Pair-fed control rats had a much lower incidence of teratogenesis, thereby implicating a direct role of zinc deficiency rather than decreased growth rates in causing the abnormalities.

Studies investigating the cause of zinc-deficiency-induced teratogenesis have shown that the uptake of tritiated thymidine in 12-day-old rat embryos is severely depressed due to zinc deficiency (71). Thymidine kinase activity was markedly decreased in 15-day-old, zinc-deficient rat embryos as compared with that in pair-fed controls (72). Further, DNA polymerase, a zinc metalloenzyme, showed decreased activity in zinc-deficient rat embryos, and hepatic DNA-dependent RNA polymerase activity of prenatally zinc-deficient suckling rats was similarly decreased (73, 74). Hurley (75) suggested that the teratogenesis in zinc deficiency is probably due to impaired synthesis of nucleic acids which, in turn, results in alterations in differential rates of growth, in addition to chromosomal alterations that may also be involved.

Warkany and Petering (76) repeated Hurley's zinc deficiency studies in pregnant rats but conducted extensive microscopic sectioning of fetal tissues of the brain. They reported a number of eye anomalies, including cataract, coloboma, and absence or interruption of the optic nerve. Optic chiasm was absent when the optic nerves were missing and the chiasm was asymmetrical when only one optic nerve was connected to the brain.

Because vitamin A deficiency is also reported to be teratogenic (77-79), Duncan and Hurley (80) studied the results of combined vitamin A and zinc deficiency in pregnant rats. Deficiency of both nutrients produced teratogenicity greater than that predicted by an additive effect; this effect seemed to result from an interaction between the two nutrients. Excess vitamin A also caused

gross malformations of the fetus, particularly the eye When Eckhert and Hurley (81) studied the combination of zinc deficiency and vitamin A excess in pregnant rats, they found no evidence for a teratogenic interaction between the two. Synthesis of DNA was not reduced when vitamin A excess was induced, but this reduction did occur with zinc deficiency. These data show separate mechanisms of teratogenic action for zinc deficiency and vitamin A excess.

Substantiating data in humans for zinc deficiency as a cause of congenital malformations are unavailable. One recent report, however, of an 18-year-old woman who delivered an anophthalmic baby raised the question of zinc's role in the malformation (82). On approximately days 49 to 54 of pregnancy, the mother consumed only "fruit juices and soda crackers with a periodic glass of milk." Subsequently, her diet returned to normal. No serum zinc levels were drawn at this time, but at delivery, hair zinc levels were measured. These levels indicated normal hair zinc near the scalp and at the end of shaft although the middle zone had a decreased zinc concentration. The authors (82) suggest that serum zinc dropped at a critical stage of ocular development but after a return to a normal diet, the zinc level rose sufficiently in the mother to carry the fetus to term. Although these data are speculative and suspect because of poor correlation between zinc status and hair zinc levels, and the lack of a high incidence of ocular malformations in countries where poor maternal diets are the rule rather than the exception, they provide an interesting concept when coupled with Hurley's data from rats.

In 1973, Jones and coworkers (83) described the fetal alcohol syndrome in infants born to alcoholic mothers. One of the principal features of fetal alcohol syndrome is short palpebral fissures, which may reflect developmental microophthalmia. Other associated ocular features include ptosis, strabismus, epicanthal folds, myopia, blepharophimosis, and clinical microophthalmia (84). Although substantial data indicate that ethanol is teratogenic, there is no firm data to implicate nutritional factors important in this syndrome. However, zinc deficiency is suspect as a teratogenic factor because zinc is often deficient in alcoholic patients (14, 85, 86).

Recently Flynn and associates (87) measured maternal plasma zinc and fetal cord zinc levels in 25 alcoholic and 25 nonalcoholic patients. Both maternal zinc and fetal cord-plasma zinc levels were significantly lower for alcoholic than for nonalcoholic mothers. Infants of alcoholic mothers had slightly more defects (18 of 25) than those of the nonalcoholic group (14 of 25) and the defects "more closely resembled" those of fetal alcohol syndrome. A strong inverse correlation was found between maternal zinc levels and congenital abnormalities in the babies. The correlation between fetal zinc and birth defects was less clear. Ocular abnormalities were three times commoner in the children of alcoholic (6 of 25) than in those of nonalcoholic women (2 of 25). Although the group sizes are small in this study and although no child of an alcoholic mother actually had the fetal alcohol syndrome, the role of zinc in this syndrome deserves more attention and further study.

Table 1 Hypotheses for the Mechanism of Impairment of Taste Acuity in Zinc Deficient Experimental Animals*

Diminished protein synthesis in taste bud cells
Reduced alkaline phosphatase activities in taste buds
Alteration of a zinc-containing salivary protein
Central nervous system dysfunction
Blockage of the taste pore region of the taste bud

* Modified from Catalanotto and Nanda (91)

Gustatory Acuity

OBSERVATIONS IN EXPERIMENTAL ANIMALS

Early investigation in this field came from the Neuroendocrinology Laboratory of the National Institutes of Health under the leadership of Dr. Robert Henkin. In 1972, Catalanotto and Henkin (88) showed that penicillamine-fed rats had a greater preference for saline than for pure water, as did rats fed excessive dietary concentrations of cystine. Common to both chemicals is the exposed sulfhydryl (thiol) group. Because of the recognized effects of penicillamine on copper metabolism, however, these effects were initially ascribed to depletion of copper. Two years later, McConnell and Henkin (89) reported that zinc deficiency in rats produced a similar alteration in the preference for saline solutions over water. More recently, Catalanotto and Lacy (90) showed that not only preference for sodium chloride, but also preference for sucrose, quinine, and hydrochloric acid, were altered in experimental zinc deficiency in rats. Some physiologists have generally assumed that in animals a preference for a chemical tastant shows altered taste acuity (88), but this finding has not been proved.

Various mechanisms for the zinc-deficiency-induced reduction in taste acuity have been advanced (Table 1). Catalanotto and Nanda (91) found morphologic disruption of the epithelium of taste bud structures in zinc-depleted rats, but no alteration in the pore area consistent with the blockage-of-taste-bud hypothesis.

SALIVA, TASTE, AND ZINC

That changes in salivary secretions alter taste function is an intriguing hypothesis. Chaudry and Meyer (92) showed a 60% reduction in alkaline phosphatase activity in the submandibular gland of zinc-deficient rats, and implicated nutritional damage in the myoepithelial cells of the salivary glands—the primary source of this enzyme—in the genesis of taste disorders with zinc deficiency. Everett and Apgar (93) found that zinc deficiency in adult rats of both sexes and in pregnant animals did not diminish the zinc concentration in whole saliva. As reviewed by Freeland-Graves and associates (94), clinical pathologists and nutritionists have measured zinc concentration throughout the years in attempts to correlate it with specific pathologic states or with nutritional deficiencies. If taste acuity were a consequence of zinc deficiency in humans, its mediation through an alteration in salivary composition would be a logical possibility. In contrast to the observations of Everett and Apgar (93), Freeland-Graves and associates (94), and Greger and Sickles (95)

Table 2 Tastant Concentrations in the Three Drop Forced Choice Dilution Technique*

Sodium Chloride (Salty)	Sucrose (Sweet)	Hydrochloric Acid (Sour)	Urea (Bitter)
6	6	0 5	60
12	12	0.8	90
30	30	3	120
60	60	6	150
90	90	15	300
150	150	30	500
300	300	60	800
500	500	90	1000
800	800	150	2000
1000	1000	300	5000
3000	3000	500	...

* From Henkin and associates (99)

reported reductions in zinc concentration in whole saliva or in the sediment of centrifuged samples of saliva paralleling other indices of zinc nutriture. In a prospective study of seven college women, Freeland-Graves and colleagues (96) showed a serial decrement in whole-saliva zinc content during 3 weeks of an enforced vegetarian diet. Henkin and associates (97) compared the salivary zinc concentrations in samples taken directly from the parotid gland. Patients with idiopathic hypogeusia (impaired taste acuity) had consistently lower salivary zinc levels than did controls. Moreover, administration of radioisotopic zinc showed a concentration of zinc by the parotid gland. Henkin and associates (98) showed that the parotid gland produced a 37 000 dalton zinc metalloprotein with 2 g atoms of zinc per mol. Because of its putative role in taste function, this protein was termed "gustin."

Human saliva appears to contain measurable amounts of zinc; the zinc content seems to change with other indices of zinc nutriture; and it may be contained, in part, in a zinc metalloprotein. However, because the exact role of saliva in the taste process of mammals is not fully understood, these observations cannot be related to hypotheses regarding the pathogenesis of hypogeusia taste abnormalities in zinc deficiency.

ZINC-RESPONSIVE HYPOGEUSIA

In the early 1970's, preliminary evidence was produced that zinc treatment could improve hypogeusia in some specific instances (99). For example, administration of zinc corrected the taste impairment of a patient who had been treated for cystinuria with penicillamine (100). Henkin and associates (101-103) reported the initial experience with 103 patients with symptoms of decreased taste acuity. Objective taste acuity assessment using the three-drop forced-choice dilution technique (Table 2) showed elevated detection and recognition thresholds in the symptomatic patients: 73% had elevated thresholds with sodium chloride (salty); 48% with sucrose (sweet); 97% with urea (bitter); and 98% with hydrochloric acid (sour). As compared to 99 $\pm$ 2 μg/dL (mean $\pm$ SE) in 95 control subjects, the mean serum zinc concentration was 76 $\pm$ 1 μg/dL ($p < 0.001$). Thirty-one patients with idiopathic hypogeusia had zinc levels less than 70 μg/dL as compared to 2 persons in the control group. Conversely, 2 hypogeusic patients and 39 controls had zinc concentrations above 100 μg/dL. A single-blind, placebo-zinc crossover supplementation was done in 47 of the patients with hypogeusia. Patients were given placebo capsules for intervals from 1 to 4 weeks, and then switched to either 6.25 mg or 25 mg of zinc four times per day. The physician, but not the patient, knew the true identity of the medication being dispensed. The lower dose of zinc (25 mg/d) caused a slight, but significant, improvement in taste acuity; 100 mg of zinc daily produced normal restoration in over 50% of all taste thresholds for each of the four tastant qualities. It is of note that in addition to depressed taste acuity, a large number of the patients with idiopathic hypogeusia also had symptoms of unpleasant tastes (dysguesia) expressed as abhorrent, obnoxious taste sensations, persistence of taste perceptions in the absence of stimuli, and inappropriate taste qualities.

Further impetus was given to the notion that taste impairment could be improved by zinc supplementation by observations on children from Denver, Colorado. Among 132 children between 4 and 17 years of age from white, middle-class homes, 10 had hair zinc concentrations in the markedly deficient range of under 70 μg/g. A more intensive examination of this subgroup showed a height below the 10th percentile in 8, and a history of poor appetite in 7. Hambidge and associates (104) tested taste thresholds by a modification of the three-drop forced-choice hypogeusia in terms of elevated detection or recognition in five subjects. These subjects had a therapeutic trial with zinc, 1 to 2 mg/kg·d for 1 to 3 months; each child achieved normal taste thresholds at the conclusion of the trials.

In none of the aforementioned studies was a double-blind, randomized design used, nor was a control group simultaneously subjected to the same treatment. However, scientific interest in the possibility that human zinc deficiency adversely affected gustatory acuity was awakened. This interest led to clinical observations aimed at documenting both the incidence of taste impairment in patients with zinc deficiency, and the application of taste threshold assessment as a functional index of zinc nutriture.

CLINICAL OBSERVATIONS IN HUMANS

Since the initial demonstration of zinc-responsive taste impairment, many clinical observations on the association of zinc status and gustatory function have been reported. Some reports are highly circumstantial. Zinc deficiency has been seen in chronic and acute liver diseases, including alcoholic cirrhosis and viral hepatitis (105, 106). Burch and associates (107) found objective hypoguesia characterized by elevated recognition and detection thresholds for at least one taste quality in eight men with alcoholic cirrhosis. Although serum zinc levels were reportedly determined, no comment on the zinc status of the subjects was made. Smith and associates (108) evalu-

ated detection and recognition thresholds and forced scaling of intensity for the four taste qualities in 22 patients with acute viral hepatitis and 16 patients with chronic liver disease (alcoholic cirrhosis, chronic active hepatitis). Mean zinc concentrations were 59 ± 5 μg/dL (mean ± SE) in early hepatitis, 81 ± 8 μg/dL in late hepatitis, and 32 ± 3 μg/dL in chronic liver disease. Detection and recognition thresholds and scaling were uniformly abnormal in chronic liver disease and in the early phases of hepatitis, but taste performance returned toward normal in late, convalescent hepatitis. No clear correlation between serum zinc and gustatory function was seen in this study.

Taste abnormalities have been found in patients receiving systemic chelating agents. Penicillamine (β, β dimethylcysteine) is a chelating agent that can increase the urinary excretion of copper and other divalent cations including zinc. Subjective taste impairment or objective hypogeusia as measured by the three-drop forced-choice method have been reported in patients receiving penicillamine therapy (99, 109, 110). The gustatory defects appeared in 32% to 35% of persons in whom the drug was prescribed for scleroderma, rheumatoid arthritis, cystinuria, and idiopathic pulmonary fibrosis, but in only 4% of patients receiving the drug for Wilson's disease (110-113). This finding led to the speculation that copper depletion was the cause of hypogeusia with penicillamine (109-114). Because zinc depletion is also produced by penicillamine treatment, it has been suggested that zinc deficiency is the mechanism (54, 110, 115). In one patient with cystinuria treated with this drug, a fall in circulating zinc concentration and complete loss of taste sensation coincided, and zinc therapy restored both to normal (110). Knudsen and Weismann (116) studied nine patients with generalized scleroderma and one patient with rheumatoid arthritis for 4 months after initiation of penicillamine treatment. Serum and urinary zinc and copper levels and taste detection thresholds for salty, sweet, bitter, and sour were monitored. There was decreased acuity for each of the taste qualities, but serum zinc and urinary zinc levels remained unchanged. Urinary copper excretion increased during treatment, and the magnitude of hypercupiuria paralleled the changes in taste perception.

Another systemic chelating agent, histidine, has been studied in relation to zinc status and taste acuity (117), in conjunction with a therapeutic trial of pharmacologic doses of this amino acid in progressive systemic sclerosis. Dosages ranged from 32.4 to 64.8 g/d for 8 to 12 days. Patients developed anorexia and subjective taste disorders. The treatment caused to tenfold increase in urinary zinc excretion accompanied by marked reduction in mean serum zinc concentrations from 78 ± 7 to 48 ± 3 μg/dL (mean ± SE). Objective taste thresholds were elevated for all tastants as compared to pretreatment performance, but reversed within 24 hours of zinc administration (100 mg of elemental zinc) despite continuation of histidine therapy.

Taste acuity was studied in 19 patients with thermal burns covering from 5% to 75% of the body surface (118). Mean serum zinc values were 68 ± 3 μg/dL (mean ± SE) as compared to 99 ± 2 μg dL for controls, and most patients had hyperzincuria. Using the three-drop forced-choice technique, objective evidence of hypogeusia was found in 16 of 19 subjects. Casper and associates (119) examined the role of taste disorder and zinc nutriture in 30 patients with anorexia nervosa. Mean taste recognition thresholds were elevated in the anorexic patients with particular deficiencies in the recognition of the sour tastants. Plasma zinc concentration (71.9 ± 14.3 μg/dL, mean ± SD) was moderately, but significantly deficient as compared to controls (83.3 ± 9 μg/dL, $n = 32$). Urinary zinc excretion was also depressed, and correlated with plasma zinc levels. Mean hair zinc content was within the normal range. Taste recognition threshold scores did not correlate with plasma zinc. Taste performance improved in the nine patients tested after nutritional repletion.

Taste acuity as shown by quantitatively elevated detection or recognition thresholds is often reduced in chronic renal failure (120). Various abnormalities of circulating zinc or hair zinc have been found in patients with uremia-induced hypogeusia (121-125), although normal zinc levels were found in one series of patients (126). Mahajan and associates (123) found a correlation between plasma zinc concentrations and salt recognition thresholds, but other reports have failed to correlate taste acuity indices with static parameters of zinc status (122, 125). Hemodialysis treatments, per se, improved or corrected hypogeusia, but no parallel effect of dialysis on circulating zinc levels was seen (121, 122, 125).

Evidence for zinc deficiency as a frequent complication of Crohn's disease (regional enteritis; granulomatous ileitis and colitis) of the intestine, including depressed circulating zinc levels, low hair levels of zinc, and decreased urinary zinc excretion has been reported (127-131). Solomons and associates (127), using the three-drop forced-choice technique, found impaired taste acuity as compared to controls in adult patients with active Crohn's disease ($p < 0.001$) and in growth-retarded adolescents ($p < 0.001$) (127). Similarly, in 10 patients with celiac sprue and a mean reduction in plasma zinc, taste acuity thresholds were elevated as compared to healthy adult controls ($p > 0.01$) (132).

Cystic fibrosis is another disease that predisposes to zinc depletion (133-135). Some patients with this disorder are in negative zinc balance due to reduced absorption of dietary zinc (136). Cystic fibrosis is also a disease that has aroused interest of taste physiologists. Henkin and Powell (137) reported increased taste acuity in patients with cystic fibrosis, whereas other investigators have found taste acuity to be normal or subnormal (135, 138-141). The zinc status of patients in some of these studies was not evaluated. Palin and colleagues (142) assessed zinc nutriture in a cohort of cystic fibrosis patients along with an evaluation of taste acuity. Plasma and hair zinc concentrations were normal in these patients. Taste acuity was also normal, and did not change during a 2-month course of zinc supplementation. Solomons and associates (135) found impaired detection and

recognition in a group of 19 patients with cystic fibrosis. These patients also had low hair zinc concentrations, although plasma zinc levels were normal. The hypogeusia of patients with cystic fibrosis may have its origin in disordered zinc metabolism.

Storms and coworkers (143) used the three-drop forced-choice dilution technique to evaluate taste in 18 adult patients with chronic pancreatitis, another cause of pancreatic insufficiency. In fact, half of the subjects had steatorrhea. As compared to 15 age-matched controls, the patients' detection thresholds for salty and sweet and recognition thresholds for salty, sweet, and sour were elevated. Zinc in plasma and saliva were measured, and found to be equivalent in patients and controls. Treatment with pancreatic extract for a month resulted in improved taste acuity.

Greger and Sciscoe (144) studied 44 elderly persons (mean age, 79 years; range, 52 to 89) in an urban feeding program. A forced-choice triangle test for recognition of saltiness was done using salt in mmol concentrations of 6, 12, 24, and 48. The mean detection threshold, 23.4 ± 2 mmol, did not differ from the 16.4 ± 1.9 mmol threshold of a local control group with an average age of 27 years, but was higher than that reported by other investigators using similar (but not identical) procedures. Seven of the subjects had a detection threshold greater than 48 mmol salt, whereas none of the controls failed to detect the 24 mmol solution. No correlations between taste acuity and either dietary zinc intake or hair zinc levels were seen. These findings were essentially repeated in a subsequent survey of elderly persons from the same region as part of a zinc supplementation study (145).

A recent report from Yugoslavia by Buzina and coworkers (146) comes closest to reproducing the original observations of Hambidge and associates (104) with respect to an association between low hair zinc concentrations and hypogeusia. In this study, children 9 to 12 years of age were evaluated for plasma zinc, hair zinc, taste acuity (using a forced-choice dilution triangle test), and anthropometric classification; the cumulative percentage of children with hair zinc below 70 μg/g in this sample was 35%. Twenty-one of the 76 children having measurements of both hair and plasma zinc and taste perception were hypogeusic; hair zinc, but not plasma zinc, concentrations differed significantly between the children with normal taste sensitivity and those with impaired taste sensitivity ($p = 0.05$). The population was admittedly chosen from a nutritionally deprived sector, but this study seems to verify the association of impaired taste and zinc deficiency in a population at large.

MANIPULATION OF ZINC NUTRITURE

Clinical observations essentially attempt to correlate taste acuity or other taste perception qualities with biochemical indices of zinc nutriture. However, the lack of reliability of zinc indicators in showing total-body zinc status limits them as reference standards for taste performance. A more definitive approach would involve the manipulation of nutritional status, either zinc depletion or zinc supplementation, to better characterize and define zinc nutriture. Both of these strategies have been used in the investigation of taste.

Wright and associates (147) studied taste in six male volunteers who underwent a zinc depletion experiment in the metabolic unit at the University of California at Berkeley. The subjects ranged in age from 21 to 30 years, and were studied during the initial phase, with a daily zinc intake of 15 mg, and in the depletion phase, on a zinc intake of 0.25 mg, after their plasma zinc concentrations had fallen below 70 μg/dL, and in three subjects, after repletion with a 15 mg zinc intake. Subjects tasted 30 mL volumes of four concentrations of sodium chloride and urea solutions, and two distilled water blanks. Intensity ratings for the lower two concentrations for saltiness were altered during depletion. The more concentrated salty qualities, and all of the bitter solutions were scored identically despite nutritional manipulation. In the three subjects, restudied during repletion, there was a tendency toward recovery of basal intensity perception for the lower concentrations of the sodium chloride solution. The changes in taste perception were not correlated with the change in plasma zinc, with parotid saliva zinc concentration, nor with the length of time on the depletion diet.

ZINC SUPPLEMENTATION

The opposite approach to manipulating zinc status is zinc supplementation of persons with presumed impairment of zinc nutriture. Weismann and associates (54) conducted a randomized, double-blind supplementation trial with oral zinc in 30 Danish patients with stable alcoholic cirrhosis confirmed by biopsy results. Sixteen subjects received 45 mg of zinc daily as zinc sulfate while 14 received a placebo. The duration of the trial was 6 weeks. A modification of the three-drop forced-choice test was used. Mean taste score improved from 7.4 to 10.2 (arbitrary units) in the zinc-treated group ($p < 0.001$), but was unaffected by the placebo, 7.8 before and 9.0 after the trial ($p < 0.1$). Supplementation was accompanied by a rise in mean serum zinc from 86 to 113 μg/dL in the zinc cohort; mean zinc levels were stable at 81 and 83 μg/dL in the placebo-treated group. The taste function results are interesting in view of the good nutritional status and normal circulating zinc values of the subjects. Except for the traditional association of cirrhosis with zinc depletion, there was little reason to suspect a prevalence of zinc deficiency from the pretreatment findings in either group of patients (105).

Palin and associates (142) conducted a double-blind supplementation study among children with cystic fibrosis using patients' unaffected siblings as controls. A three-drop forced-choice dilution technique was used to assess taste acuity before and after an 8-week supplementation period. Sixteen patients and seven sibling controls received zinc sulfate, 23 mg, and 20 patients and eight controls received placebo. Taste acuity in patients was normal before supplementation, and was unaffected by the type of treatment. Similarly, plasma zinc concentration and hair zinc levels were identical for patients and siblings, and unresponsive to supplementation of either kind. As in the study by Weismann and coworkers (54),

the static indices of zinc nutriture gave little indication of zinc deficiency among the patients selected, and hence, there was little margin for a nutritional response

The response of gustatory function to zinc supplementation in hemodialyzed uremic patients had been assessed by a number of investigators. Mahajan and colleagues (124) in a non-blinded, 6-week supplementation trial with zinc acetate, 50 mg/d, saw the correction of elevated salt, sweet, and bitter, but not sour, detection and recognition thresholds in 11 patients receiving regular hemodialysis. These same investigators did a subsequent double-blind study in 22 patients randomized to receive 25 mg of zinc as acetate or a sucrose placebo for 6 to 12 weeks. Once again, elevated thresholds were normalized in the zinc-treated subjects, but placebo treatment had no effect of taste acuity. Atkin-Thor and associates (125) did a double-blind, cross-over study in which subjects were prescribed zinc sulfate, 170 mg three times per week, or a placebo for 6-week periods, each in a randomized sequence. Hair zinc and plasma zinc levels rose, and taste thresholds improved during the zinc treatment-periods. Subjective taste perception was assessed in ten hemodialyzed uremic men before and after randomized treatment with modifidation of the zinc content of the dialysis bath for 4 weeks. In five subjects' regimen, 400 μg/L of zinc was added to the dialysate. Zinc did not affect plasma zinc concentrations, but, paradoxically, subjects in the placebo group reported enhanced subjective taste perception during the trial.

Greger and Geissler (145) gave elderly institutionalized persons either a placebo ($n = 24$) or a capsule containing 15 mg of zinc ($n = 25$), served before the noonday meal for 95 days. Taste detection and recognition thresholds for salt and sucrose were studied before and after the supplementation period using the same forced-choice triangle design as in the previous study (144). The detection and recognition thresholds were equivalent for the two treatment groups at the beginning of the trial. Recognition thresholds were unaffected, but there was a tendency (not statistically significant) toward improvement of detection thresholds for both salty and sweet in the group receiving zinc. The only change of statistical significance was a deterioration in the recognition of sucrose in the placebo group, as compared to basal performance ($p < 0.011$). Hair zinc levels increased significantly ($p < 0.002$) in the group that received the zinc supplement.

Given the promise of the single-blind experience with zinc supplementation in idiopathic hypogeusia (102, 103), Henkin and associates (148) did a randomized, double-blind, semi-crossover study in 106 patients with taste and smell dysfunction (148). The patients were distributed at random into four groups for two consecutive 3-month treatment periods. One group received zinc, 100 mg/d, for both periods; another group received placebo throughout; a third group received zinc supplementation followed by placebo; and a final group received placebo followed by zinc. The quantification of taste abnormalities was identical to that in the previously reported trial. Before treatment, mean serum zinc levels for all groups was significantly below normal, and urinary zinc excretion was within normal limits Leukocyte alkaline phosphatase levels were 17 U as compared to 71 U in controls ($p < 0.001$). A significant increase in serum zinc concentration and in urinary zinc excretion was seen during each period in which zinc was administered No changes were registered with placebo treatments. Analysis of the taste acuity and forced scaling performance, however, showed no significant effect of zinc sulfate as compared to placebo. Significant improvement in a number of taste indices has been seen with either zinc or placebo.

Clearly, zinc deficiency alters taste perception in animals and in humans. Zinc-responsive taste abnormalities have been shown in conditions that predispose to zinc depletion. Most age-related and idiopathic taste disorders do not appear to be caused by zinc deficiency. As an assessment index for zinc nutriture, the sensitivity and specificity of taste acuity testing, or taste intensity scaling have yet to be properly defined. Undoubtedly, taste indices will not be very specific, but for severe zinc deficiency, some alterations in taste acuity may be detectable. Other approaches to physiologic testing of gustatory function, however, may be required to comprehensively examine the role of zinc nutrition in taste. (These approaches may include intensity scaling procedures and taste preference determinations in the supra threshold range where most foods would be registered. To date, these approaches have not been used extensively in nutritional assessment.)

Olfactory Acuity

In conjunction with some of the studies involving taste acuity, there have been a small number of observations on olfactory acuity that raise the possibility that smell may also be impaired in zinc deficiency. In fact, the syndrome first reported by Henkin and associates (101) was entitled "idiopathic hypogeusia with dysgeusia, hyposmia and dysosmia" because 28 of the original 35 subjects spontaneously reported some alteration in olfactory perception. Objective assessment of olfactory acuity involved a three-stimulus, forced-choice dilution technique with various concentrations of three pungent chemicals: pyridine (onion and garlic odor); nitrobenzene (bitter almond odor); thiophene (burnt rubber odor). The procedure is analogous to the taste test used in the same laboratory. Mean detection and recognition thresholds were elevated in most subjects. Many subjects also reported dysosmia, persistent obnoxious odors. A response of abnormalities of smell to zinc therapy was reported, but specific figures were not given (101). Kreuger and Kreuger (149) reported a case of idiopathic hyposmia and dysosmia in a 67-year-old man with a history of alcoholism. The patient's serum zinc level was 77 μg/dL. Therapeutic administration of zinc, 150 mg/d for a month increased circulating zinc levels to 139 μg/dL, and produced subjective improvement of the smell-related symptoms. No formal, objective olfactory acuity testing was undertaken.

Burch and associates (107) found elevated olfactory thresholds for at least one of the odors—nitrobenzene,

thiophene, or pyridine—among his cirrhotic subjects, but no information on zinc status was reported. Vreman and associates (122) found a slight, but not significant, elevation in smell thresholds for pyridine in male uremic patients on chronic hemodialysis, these same patients had a significantly reduced mean plasma zinc concentration. All of the six patients with progressive systemic sclerosis receiving the pharmacologic doses of histidine began the trial with normal olfactory acuity, became hyposmic during treatment, but corrected with the 1-day, 100 mg zinc therapy, despite continuance of the histidine (118).

As with the taste acuity findings, Henkin and associates (148) were unable to show any differential effect of zinc sulfate or placebo on the objective hyposmia in their randomized, double-blind, crossover trial of zinc supplementation in patients with idiopathic taste and smell dysfunction (148). It would appear that, as with taste, the idiopathic loss of olfaction is not likely to be a consistently zinc-responsive condition. The balance in clinical observations reviewed, however, suggests that some forms of acquired zinc deficiency may be associated with an olfactory disorder that responds to the correction of the underlying nutritional depletion.

Conclusion

Assessment of zinc nutritional status is complex. Many of the studies cited in this review have relied on plasma or serum zinc levels only as reflective of body zinc status, which may not be valid (150-152). Caution should be exercised in interpreting the results of such studies. Moreover, many investigations of zinc and sensory function have been done as open trials, which limits the interpretation one can make from these studies. Nevertheless, zinc nutriture appears to have implications for at least three components of the mammalian sensory system: vision, olfaction, and taste. Strong evidence supports the development of zinc-responsive night blindness and hypogeusia in clinical zinc deficiency states, and it is likely that impaired color discrimination and decreased smell acuity may also develop with human zinc depletion. Interactions of zinc and vitamin A appear to be at the basis of the retinal effects of zinc deficiency (1, 28). Given the role of vitamin A in the structural and physiological integrity of mucosal epithelia, and the fact that vitamin A deficiency affects taste and smell (153, 154), closer attention to the possibilities of zinc-vitamin A interactions and the gustatory and olfactory consequences of disordered zinc metabolism, is warranted.

The search for human correlates of ocular teratogenesis, shown extensively in experimental gestational zinc deficiency, should be pursued. This search takes on additional relevance in light of the mounting suggestions that human fetal alcohol syndrome may be conditioned by maternal zinc deficiency (155).

Finally, the association of impaired sensory function and human zinc deficiency bears on the diagnostic assessment of zinc nutriture. Conventional biochemical indices of zinc status, based on measurement of zinc concentration in tissue or body fluids, are notoriously unreliable (150, 151). Recent evidence suggests that leukocyte zinc may provide a more accurate assessment of body zinc stores (156). The complementation of biochemical indices with functional indicators of zinc status would fortify this area of clinical nutritional assessment. This objective is embodied in much of the research on sensory function and zinc metabolism. Improved understanding of the interrelationships will promote the development of increasingly reliable assessment techniques for quantifying human zinc nutriture.

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References

1. Solomons NW, Russell RM. The interactions of vitamin A and zinc: implications for human nutrition. *J Clin Nutr.* 1980;33:2031-40.
2. Tucker HF, Salmon WD. Parakeratosis or zinc deficiency disease in the pig. *Proc Soc Exp Biol Med.* 1955;88:613-6.
3. Luecke RW, Hoefer JA, Brammell WS, Thorp F Jr. Mineral interrelationships in the parakeratosis of swine. *J Animal Sci.* 1956;15:347-51.
4. Prasad AS, Miale A, Farid Z, Sandstead HH, Schulert AR. Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism and hypogonadism. *J Lab Clin Med.* 1963;61:537-49.
5. Welsh SO, Marston RM. Zinc levels of the U.S. food supply 1909-1980. *Food Technol.* 1982;36:70-6.
6. Davies NT. Studies on the absorption of zinc by rat intestine. *Br J Nutr.* 1980;43:189-203.
7. Antonson DL, Barak AJ, Vanderhoof JA. Determination of the site of zinc absorption in rat small intestine. *J Nutr.* 1979;109:142-7.
8. Evans G, Grace C, Votava H. A proposed mechanism for zinc absorption in the rat. *Am J Psychol.* 1975;228:501-5.
9. Song MK, Adham NF. Role of prostaglandin E_2 in zinc absorption in the rat. *Am J Physiol.* 1979;234:E99-E105.
10. Spencer H, Kramer L, Osis D. Zinc balance in humans. In: Prasad AS, ed. *Clinical Biochemical and Nutritional Aspects of Trace Elements.* New York, Allan R. Liss, Inc., 1982:103-15.
11. American Medical Association, Department of Foods and Nutrition. Guidelines for essential trace element preparations of parenteral use: a statement by an expert panel. *JAMA.* 1979;241:2051-4.
12. Solomons NW. Biological availability of zinc in humans. *Am J Clin Nutr.* 1982;35:1048-75.
13. Prasad AS. *Zinc in Human Nutrition.* Boca Raton, Florida: CRC Press, Inc., 1977:1-80.
14. Sullivan JF, Lankford HG. Zinc metabolism and chronic alcoholism. *Am J Clin Nutr.* 1965;17:57-63.
15. Sullivan JF, Heaney RP. Zinc metabolism in alcoholic liver disease. *Am J Nutr.* 1970;23:170-7.
16. Halsted JA, Hackley B, Rudzki C, Smith JC Jr. Plasma zinc concentration in liver diseases: a comparison with normal controls and certain other chronic diseases. *Gastroenterology.* 1968;54:1098-105.
17. Prasad AS, Schoomaker EB, Ortega J, Brewer GJ, Oberleas D, Oelshlegel FJ. Zinc deficiency in sickle cell disease. *Clin Chem.* 1975;21:582-7.
18. Jayarajan P, Reddy V, Mohanram M. Effect of dietary fat on absorption of β carotene from green leafy vegetables in children. *Indian J Med Res.* 1980;71:53-56.
19. Olson JA. The effect of bile and bile salts on the uptake and cleavage of β-carotene into retinol ester (vitamin A ester) by intestinal slices. *J Lipid Res.* 1964;5:402-408.
20. Deshmukh D, Ganguly J. Effect of dietary protein contents on the intestinal conversion of Beta-carotene to vitamin A in rats. *Indian J Biochem.* 1964;1:204-7.
21. Kamath SK, Arnrich L. Effect of dietary protein on the intestinal biosynthesis of retinol from ^{14}C-β-carotene in rats. *J Nutr.* 1973;103:202-6.
22. El-Gorab MI, Underwood BA, Loerch JD. The roles of bile salts in the uptake of β carotene and retinol by rat everted sacs. *Biochim Biophys Acta.* 1975;401:265-77.
23. Takruri HRH, Thurnham DI. Effect of zinc deficiency on the conversion of β-carotene to retinol as indicated by liver stores [Abstract]. *Proc Nutr Soc.* 1982;41:53A.
24. DeLuca L, Glover J, Heller J, Olson J, Underwood B. *Guide-*

lines For The Eradication of Vitamin A Deficiency and Xerophthalmia Washington D C Nutrition Foundation 1977
25 KANAI M, RAZ A, GOODMAN DS Retinol binding protein the transport protein for vitamin A in human plasma *J Clin Invest* 1968 47:2025-44
26 RAZ A, SHIRATORI T, GOODMAN DS Studies on the protein protein and protein ligand interactions involved in retinol transport in plasma *J Biol Chem* 197 245:1903-12
27 PETERSON PA, BERGGARD I Isolation and properties of a human retinol transporting protein *J Biol Chem* 1971 246:25 33
28 SMITH JC JR, BROWN E, CASSIDY W Zinc and vitamin A interrelationships In BREWER GJ, PRASAD AS eds *Zinc Metabolism Current Aspects in Health and Disease* New York Alan R Liss, Inc, 1977 29-44
29 TARWOTJO I, SOMMER A, SOEGIHARTO T, SUSANTO D, MUHILAL. Dietary practices and xerophthalmia among Indonesian children *Am J Clin Nutr* 1982 35:574-81
30 HELLER J Transport of retinol to ocular tissues an overview *World Rev Nutr Diet* 1978 31:42-4
31. PETERSON PA, RASK L, OSTBERG L, ANDERSON L, KAMWENDO F, PERTOFT H Studies on the transport and cellular distribution of vitamin A in normal and vitamin A-deficient rats with special reference to the vitamin A-binding plasma protein *J Biol Chem* 1973 248:4009-22.
32. LEURE-DUPREE AE Electron-opaque inclusions in the rat retinal pigment epithelium after treatment with chelators of zinc *Invest Ophthalmol Vis Sci* 1981 21:1-9.
33. WALD G The synthesis from vitamin A, of "retinene$_1$" and of a new 545 mu chromogen yielding light-sensitive products *J Gen Physiol.* 1947-48,31:489-504
34 WALD G The interconversion of the retinenes and vitamins A *in vitro*. *Biochimica et Biophysica ACTA* 1950 4:215-28
35. BLISS A The equilibrium between vitamin A alcohol and aldehyde in the presence of alcohol dehydrogenase *Arch Biochem Biophys.* 1951,31:197-204
36. HUBER AM, GERSHOFF SN Effects of zinc deficiency on the oxidation of retinol and ethanol in rats *J Nutr* 1975 105:1486-90
37. PATEK AJ JR, HAIG C The occurrence of abnormal dark adaptation and its relation to vitamin A metabolism in patients with cirrhosis of the liver *J Clin Invest* 1939 18:609-16
38 VALLEE BL, WACKER WEC, BARTHOLOMAY AF, HOCH FL. Zinc metabolism in hepatic dysfunction *Ann Intern Med* 1959 50:1077-91
39 MORRISON SA, RUSSELL RM, CARNEY EA, OAKS EV Zinc deficiency a cause of abnormal dark adaptation in cirrhotics. *Am J Clin Nutr* 1978,31:276-81
40 RUSSELL RM, MORRISON SA, SMITH FR, OAKS EV, CARNEY EA Vitamin A reversal of abnormal dark adaptation in cirrhosis study of effects on the plasma retinol transport system *Ann Intern Med* 1978,88:622 6
41 MCCLAIN C, VAN THIEL D, PARKER S, BADZIN L, GILBERT H Alterations in zinc vitamin A, and retinol binding protein in chronic alcoholics a possible mechanism for night blindness and hypogonadism Alcoholism *Clin Exp Res* 1979 3:135-41
42. WARTH JA, PRASAD AS, ZWAS F, FRANK RN Abnormal dark adaptation in sickle cell anemia *J Lab Clin Med* 1981 98:189-94
43 TOSKES PP, DAWSON W, CURINGTON C, LEVY NS, FITZGERALD C Non-diabetic retinal abnormalities in chronic pancreatitis *N Engl J Med* 1979 300:942 6
44 TOSKES P, DAWSON W, DUNCAN D, STORMS L, FITZGERALD C Treatment of n-diabetic retinopathy in patients with chronic pancreatitis [Abstract] *Clin Res* 1978 26:587A
45. TOSKES P CURINGTON C, LEVY N DAWSON W Abnormalities in retinal function in patients with chronic pancreatitis *Clin Res (Southern Section)* 1982,51A
46 TAM SW, WEBER KE, WAGNER FW Light sensitive zinc content of protein fractions from bovine rod outer segments *Biochem Biophys Res Commun* 1976,72:302-9.
47 SMITH JC JR McDANIEL EG, FAN FF, HALSTED JA Zinc a trace element essential in vitamin A metabolism *Science* 1973 181:954-5
48 SMITH JF, BROWN ED, SMITH JC JR The effect of zinc deficiency on the metabolism of retinol-binding protein in the rat *J Lab Clin Med* 1974 84:692 7
49 ETTE SI, BASU TK, DICKERSON JW T Short-term effect of zinc sulphate on plasma and hepatic concentrations of vitamins A and E in normal weanling rats *Nutr Metab* 1979 23:11-6
50 CARNEY SM, UNDERWOOD BA, LOERCH JD Effects of zinc and vitamin A deficient diets on the hepatic mobilization and urinary excretion of vitamin A in rats *J Nutr* 1976 106:1773-81
51 TAO S HURLEY LS Changes in plasma proteins in zinc-deficient rats *Proc Soc Exp Biol Med* 1971,136:165-7
52 SHINGWEKAR AG, MOHANRAM M, REDDY V Effect of zinc supplementation on plasma levels of vitamin A and retinol-binding protein in malnourished children *Clin Chim Acta* 1979 93:97-100
53 MATHIAS PM The effect of zinc supplementation on plasma levels of vitamin A and retinol binding protein (RBP) in children recovering from protein energy malnutrition (PEM) [Abstract] *Proc Nutr Soc* 1982 41 52A
54 WEISMANN K CHRISTENSEN E DREYER V Zinc supplementation in alcoholic cirrhosis a double blind clinical trial *Acta Med Scand* 1979 205:361-6
55 RUSSELL RM, CARNEY E, FLOCK K, GARRETT M, KARWOSKI P Acute ethanol administration causes transient impairment of blue-yellow color vision alcoholism *Clin Exp Res* 1980 4:396-9
56 KLINGBERG W, PRASAD A, OBERLEAS D Zinc deficiency following penicillamine therapy In PRASAD AS ed *Trace Elements in Human Health and Disease* New York Academic Press 1976, 51-65
57 YASSUR Y, SNIR M, MELAMED S, BEN-SIRA I Bilateral maculopathy simulating 'cherry-red spot' in a patient with Crohn's disease *Br J Ophthalmol* 1981,65:184-8
58 NEUDNER KH, HAMBIDGE KM Zinc therapy of acrodermatitis enteropathica *N Engl J Med* 1975 292:879-82
59 MATTA CS, FELKER GV, IDE CH Eye manifestations in acrodermatitis enteropathica. *Arch Ophthalmol* 1975 93:140-2
60 RACZ P, KOVACS B, VARGA L, UJLAKI E, ZOMBAI E, KARBUCZKY S Bilateral cataract in acrodermatitis enteropathica. *J Pediatr Ophthalmol Strabis* 1979 16:180-2
61 MOYNAHAN EJ Zinc deficiency and disturbances of mood and visual behaviour [Letter] *Lancet* 1976,1:91
62. MICHAELSSON G Zinc therapy in acrodermatitis enteropathica. *Acta Dermatol* 1974,54:377-81
63 LEOPOLD IH Zinc deficiency and visual impairment [Editorial]. *Am J Ophthalmol* 1978,85:871-5
64 STURTEVANT FM Zinc deficiency, acrodermatitis enteropathica, optic atrophy, subacute myelo-optic neuropathy, and 5, 7-dihalo-8-quinolinols *Pediatrics* 1980,65:610-3
65 EDSTROM A, MATTSON H Small amounts of zinc stimulate rapid axonal transport in vitro. *Brain Res* 1975,86:162-7
66 NICKOLSON V, VELDSTRA H The influence of various cations on the binding of colchicine by rat brain homogenates stabilization of intact neurotubules by zinc and cadmium ions *FEBS Lett* 1972,23:309-13
67 WEISMANN K, ROLD PETERSEN J, HJORTH N, KOPP H Chronic zinc deficiency syndrome in a beer drinker with a Billroth II resection *Int J Dermatol* 1976 15:757-61
68 SARAUX H, BECHELOTTE B, NOL B, COURTOIS B The diminution of the level of serum zinc during some toxic optic neuritis cases. *Ann Oculist* 1975,208:29-31
69 HURLEY LS, GOWAN J, SWENERTON H Teratogenic effects of short-term and transitory zinc deficiency in rats *Teratology* 1971,4:199-204
70 HURLEY L, SWENERTON H Congenital malformations resulting from zinc deficiency in rats *Proc Soc Exp Biol Med* 1966 123:692-6
71 SWENERTON H, SHRADER R, HURLEY LS Zinc-deficient embryos reduced thymidine incorporation *Science* 1969 166:1014-5
72 DRIOSTI IE, HURLEY LS Depressed thymidine kinase activity in zinc-deficient rat embryos *Proc Soc Exp Biol Med* 1975 150:161-5
73 DUNCAN JR, HURLEY LS Thymidine kinase and DNA polymerase activity in normal and zinc deficient developing rat embryos *Proc Soc Exp Biol Med* 1978 159:39-43
74 TERHUNE MW, SANDSTEAD HH Decreased RNA polymerase activity in mammalian zinc deficiency *Science* 1972 177:68-9
75 HURLEY LS Zinc deficiency in prenatal and neonatal development In BREWER GJ, PRASAD AS, eds *Zinc Metabolism-Current Aspects in Health and Disease* New York Alan R Liss Inc, 1977 47-58
76. WARKANY J, PETERING HG Congenital malformations of the central nervous systems in rats produced by maternal zinc deficiency *Teratology* 1972 5:319-34
77 HALE F The relation of vitamin A to anophthalmos in pigs *Am J Ophthalmol* 1935 18:1087-93
78 WARKANY J, SCHRAFFENBERGER E Congenital malformation of the eyes induced in rats by maternal vitamin A deficiency *Proc Soc Exp Biol Med* 1944 57:49-52
79 WARKANY J, SCHRAFFENBERGER E Congenital malformation induced in rats by maternal vitamin A deficiency *Arch Ophthalmol* 1946,35:150 69
80 DUNCAN JR, HURLEY LS. An interaction between zinc and vitamin A in pregnant and fetal rats *J Nutr* 1978 108:1431-8
81 ECKHERT CD, HURLEY L Influence of various levels of hypervitaminosis A and zinc deficiency on teratogenesis and DNA synthesis in the rat *Teratology* 1979,19:279-84
82 ECKHERT CD, ROSENTHAL AR Anophthalmia associated with maternal zinc status in an 18 year old mother [Abstract] In *Abstracts of the 11th International Congress of Nutrition*. Rio de Janeiro, Brasil, August 1978,205
83 JONES KL, SMITH DW, ULLELAND CN, STREISSGUTH AP. Pattern of malformation in offspring of chronic alcoholic mothers *Lancet* 1973,1:1267-71

84 Clarren SK, Smith DW. The fetal alcohol syndrome. *N Engl J Med* 1978;298:1063-7.
85 Sullivan JF. Effect of alcohol on urinary zinc excretion. *Q J Stud Alcohol* 1962;23:216-20.
86. Sullivan JF, Lankford HG. Urinary excretion of zinc in alcoholism and postalcoholic cirrhosis. *Am J Clin Nutr* 1962;10:153-7.
87 Flynn A, Martiers SS, Sokol RJ, Miller SI, Golden NL, Del Villano BC. Zinc status of pregnant alcoholic women: a determinant of fetal outcome. *Lancet* 1981;1:572-5.
88. Catalanotto FA, Henkin RI. Effects of thiols on sodium chloride preference and copper and zinc metabolism in the rat. *Am J Physiol* 1972;222:1594-8.
89. McConnell SD, Henkin RI. Altered preference for sodium chloride, anorexia and changes in plasma and urinary zinc in rats fed a zinc-deficient diet. *J Nutr* 1974;104:1108-14.
90. Catalanotto FA, Lacy P. Effect of a zinc deficient diet upon fluid intake in the rat. *J Nutr* 1977;107:436-42.
91. Catalanotto FA, Nanda R. The effects of feeding a zinc-deficient diet on taste activity and tongue epithelium in rats. *J Oral Pathol.* 1977;6:211-20.
92. Chaudhry IM, Meyer J. Response of submandibular gland of the rat to nutritional zinc deficiency. *J Nutr* 1979;109:316-20.
93. Everett GA, Apgar J. Effect of zinc status on salivary zinc concentrations in the rat. *J Nutr* 1979;109:406-11.
94. Freeland-Graves JH, Hendrickson PJ, Ebangit ML, Snowden JY. Salivary zinc as an index of zinc status, in women fed a low-zinc diet. *Am J Clin Nutr* 1981;34:312-21.
95. Greger JL, Sickles YS. Saliva zinc levels: potential indicators of zinc status. *Am J Clin Nutr.* 1979;32:1859-66.
96. Freeland-Graves JH, Ebangit ML, Hendrickson PJ. Alterations in zinc absorption and salivary sediment zinc following a lacto-ovo-vegetarian diet. *Am J Clin Nutr.* 1980;33:1757-66.
97. Henkin RI, Mueller CW, Wolf RO. Estimation of zinc concentration in parotid saliva by flameless atomic absorption spectrophotometry in normal subjects and in patients with idiopathic hypogeusia. *J Lab Clin Med* 1975;86:175-80.
98. Henkin RI, Lippoldt RE, Bilstad J, Edelhoch H. A zinc protein isolated from human parotid saliva. *Proc Natl Acad Sci (USA)* 1975;72:488-92.
99 Henkin RI, Graziadei PPG, Bradley DF. The molecular basis of taste and its disorders. *Ann Intern Med* 1969;71:791-821.
100. Henkin RI, Bradley DF. Hypogeusia corrected by Ni^{++} and Zn^{++}. *Life Sci* 1970;9:701-9.
101. Henkin RI, Schechter PJ, Hoye R, Mattern CFT. Idiopathic hypogeusia with dysgeusia, hyposmia, and dysosmia. *JAMA.* 1971;217:434-40.
102. Schechter PJ, Friedewald WT, Bronzert DA, Raff MS, Henkin RI. Idiopathic hypogeusia: a description of a single blind study with zinc sulfate. In Pfeiffer CF, ed. *International Review of Neurobiology.* New York: Academic Press, 1972: 125-40.
103. Henkin RI, Schechter PJ, Raff M, Bronzert DM, Friedwald WT. Zinc and taste activity: a clinical study including a laser microprobe analysis of the gustatory receptor area. In Ponies WJ, Strain WH, Hsu JH, Woosley RL, eds. *Clinical Applications of Zinc Metabolism.* Springfield, Illinois: Charles C. Thomas, 1974: 204-21.
104. Hambidge KM, Hambidge C, Jacobs M, Baum JD. Low levels of zinc in hair, anorexia, poor growth and hypogeusia in children. *Pediatr Res.* 1972;6:868-74.
105. Vallee BL, Wacker WEC, Bartholomay AF, Robin ED. Zinc metabolism in hepatic dysfunction. I. Serum zinc concentration in Laennec's cirrhosis and their validation by sequential analysis. *N Engl J Med* 1956;255:403-8.
106 Henkin RI, Smith FR. Zinc and copper metabolism in acute viral hepatitis. *Am J Med Sci* 1972;264:401-9.
107 Burch RE, Sackin DA, Jetton MM, Sullivan JF. Decreased acuity of taste and smell in cirrhosis [Abstract]. *Gastroenterology* 1974;67:781.
108. Smith FR, Henkin RI, Dell RB. Disordered gustatory acuity in liver disease. *Gastroenterology* 1976;70:568-71.
109 Henkin RI, Keiser HR, Jaffe IA, Sternlieb I, Scheinberg IH. Decreased taste sensitivity after D-penicillamine reversed by copper administration. *Lancet* 1967;2:1268-71.
110 Keiser HR, Henkin RI, Bartter FC, Sjoerdsma A. Loss of taste during therapy with penicillamine. *JAMA* 1968;203:381-3.
111 Jaffe IA. Effect of penicillamine on the kidney and taste. *Postgrad Med J* 1968;44(suppl):15-8.
112. Multicentre Trial Group. Controlled trial of D(-)penicillamine in severe rheumatoid arthritis. *Lancet* 1973;1:275-80.
113 Ekberg M, Jeppsson J-O, Beneberg T. Penicillamine treatment of cystinuria. *Acta Med Scand* 1974;195:415-9.
114 Henkin RI, Bradley DF. Regulation of taste acuity threshold by thiols and metal ions. *Proc Natl Acad Sci (USA)* 1969;62:30-7.
115 MacFarlane MD. Penicillamine and zinc [Letter]. *Lancet* 1974;2:962.
116. Knudsen L, Weismann K. Taste dysfunction and changes in zinc and copper metabolism during penicillamine therapy for generalized scleroderma. *Acta Med Scand* 1978;204:75-9.
117. Henkin RI, Patten BM, Re PK, Bronzert DA. A syndrome of acute zinc loss: cerebellar dysfunction, mental changes, anorexia, and taste and smell dysfunction. *Arch Neurol* 1975;32:745-51.
118 Cohen IK, Schechter PJ, Henkin RI. Hypogeusia, anorexia, and altered zinc metabolism following thermal burn. *JAMA* 1973;223:914-6.
119 Casper RC, Kirschner B, Sandstead HH, Jacob RA, Davis JM. An evaluation of trace metals, vitamins, and taste function on anorexia nervosa. *Am J Clin Nutr* 1980;33:1801-8.
120. Fornari AJ, Avram MM. Altered taste perception in uremia. *Trans Am Soc Artif Intern Organs.* 1978;24:385-8.
121. Burge JC, Park HS, Whiltlock CP, Schemmel RA. Taste acuity in patients undergoing long-term hemodialysis. *Kidney Int.* 1979;15:49-53.
122. Vreman HJ, Venter C, Leegwater J, Oliver C, Weiner MW. Taste, smell and zinc metabolism in patients with chronic renal failure. *Nephron* 1980;26:163-70.
123 Mahajan SK, Prasad AS, Lumbjon J, Abbasi AA, Briggs WA, McDonald FD. Improvement of uremic hypogeusia by zinc. *Trans Am Soc Artif Intern Organs* 1979;25:443-8.
124. Mahajan SK, Prasad AS, Lumbjon J, Abbasi AA, Briggs WA, McDonald FD. Improvement of uremic hypogeusia by zinc: a double-blind study. *Am J Clin Nutr* 1978;33:1517-21.
125 Atkin-Thor E, Goddard BW, O'Nion J, Stephen RL, Kolff WJ. Hypogeusia and zinc depletion in chronic dialysis patients. *Am J Clin Nutr.* 1978;31:1948-51.
126. Ciechanover M, Peresecenschi G, Aviram A, Steiner JE. Malrecognition of taste in uremia. *Nephron* 1980;26:20-2.
127. Solomons NW, Rosenberg IH, Sandstead HH, Vo-Khactu KP. Zinc deficiency in Crohn's disease. *Digestion* 1977;16:87-95.
128. McClain C, Soutor C, Zieve L. Zinc deficiency: a complication of Crohn's disease. *Gastroenterology.* 1980;78:272-9.
129 Sturniolo GC, Molokhia MM, Shields R, Turnberg LA. Zinc absorption in Crohn's disease. *Gut* 1980;21:387-91.
130. Fleming CR, Huizenga KA, McCall JT, Gildea J, Dennis R. Zinc nutrition in Crohn's disease. *Dig Dis Sci.* 1981;26:865-70.
131. Solomons NW, Rosenberg IH. Zinc and inflammatory bowel disease [Letters]. *Am J Clin Nutr* 1981;34:1447-8.
132 Solomons NW, Rosenberg IH, Sandstead HH. Zinc nutrition in celiac sprue. *Am J Clin Nutr.* 1976;29:371-5.
133 Dodge JA, Yassa JG. Zinc deficiency syndrome in a British youth with cystic fibrosis. *Br Med J* 1970;1:411-2.
134 Halstead JA, Smith JC Jr. Plasma zinc in health and disease. *Lancet* 1970;1:322-4.
135. Solomons NW, Rieger CHL, Jacob RA, Rothberg R, Sandstead HH. Zinc nutriture and taste acuity in patients with cystic fibrosis. *Nutr Res* 1981;1:13-24.
136. Aggett PJ, Thorn JM, Dalves HT, Harries JT, Clayton BE. Trace element malabsorption in exocrine pancreatic insufficiency. *Monogr Paediatr.* 1979;10:8-11.
137 Henkin RI, Powell GF. Increased sensitivity of taste and smell in cystic fibrosis. *Science* 1962;138:1107-8.
138. Wotman S, Mandel ID, Khotim S, et al. Salt thresholds and cystic fibrosis. *J Pediatr.* 1975;87:93-6.
139 Manlapar FC, Stein AA, Pagliara AS, Apicelli AA, Porter H, Patterson PR. Phenylthiocarbamide taste sensitivity in cystic fibrosis. *J Pediatr.* 1965;66:5-11.
140 Hertz J, Cain WS, Bartoshuk LM, Dolan TF Jr. Olfactory and taste sensitivity in children with cystic fibrosis. *Physiol Behav* 1975;14:89-94.
141 Desor JA, Maller O. Taste correlates in disease states: cystic fibrosis. *J Pediatr* 1975;87:93-6.
142 Palin D, Underwood BA, Denning CR. The effect of oral zinc supplementation on plasma levels of vitamin A and retinol-binding protein in cystic fibrosis. *Am J Clin Nutr* 1979;32:1253-9.
143 Storms L, Duncan D, Toskes P. Impaired tasted acuity in patients with chronic pancreatitis [Abstract]. *Am J Clin Nutr* 1977;32:961.
144 Greger JL, Scisco BS. Zinc nutriture of elderly participants in an urban feeding program. *J Am Dietet Assoc* 1977;70:37.
145 Greger JL, Geissler AH. Effect of zinc supplementation on taste acuity of the aged. *Am J Clin Nutr* 1978;31:633-7.
146 Buzina R, Jusić M, Sapunar J, Milanović N. Zinc nutrition and taste acuity in school children with impaired growth. *Am J Clin Nutr.* 1980;33:2262-7.
147. Wright AL, King JC, Bair MT, Citron LJ. Experimental zinc depletion and altered taste perception for NaCl in young adult males. *Am J Clin Nutr* 1981;34:848-52.

148 HENKIN RI, SCHECHTER PJ, FRIEDEWALD WT, DEMETS DL, RAFF M A doubleblind study of the effects of zinc sulfate on taste and smell dysfunction *Am J Med Sci* 1976,272:285-99
149. KREUGER KC, KREUGER WB Hypogeusia and hyposmia associated with low serum zinc levels, a case report. *J Am Med Women's Assoc* 1980,35:109-11
150 SOLOMONS NW On the assessment of zinc and copper nutriture in man *Am J Clin Nutr* 1979 32:856-71
151. DANKS DM Diagnosis of trace metal deficiency—with emphasis on copper and zinc *Am J Clin Nutr.* 1981,34:278-80
152 SANDSTEAD HH. Zinc nutrition in the United States. *Am J Clin Nutr* 1973,26:1251-60.
153 BRIGGS MH, DUNCAN RB Odour receptors. *Nature* 1961,191:1310-1
154 GARRETT MS, RUSSELL RM Abnormal taste and olfactory threshold in alcoholic cirrhosis the role of vitamin A [Abstract] *Clin Res.* 1980,28:230A.
155 The role of zinc deficiency in fetal alcohol syndrome *Nutr Rev* 1982,40:43-5
156. PRASAD AS, COSSACK ZT Neutrophil zinc: an indicator of zinc status in man [Abstract]. *Am J Clin Nutr* 1982,35:835.