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ZINC NUTRITURE AND TASTE ACUITY IN PATIENTS WITH CYSTIC FIBROSIS[1,2]

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ABSTRACT

An assessment of zinc nutriture was undertaken in 19 juvenile patients with cystic fibrosis and 40 control adolescents. Plasma zinc concentration, hair zinc content and quantitative taste acuity score were determined in each individual. In the patients, these data were related to other clinical data. No difference in plasma zinc between patients and controls was found. Moreover, no correlation between biochemical indices of zinc status and growth attainment was seen in contradistinction to a previously reported suggestion that growth-retarded patients were more prone to zinc depletion. Hair zinc was significantly lower and taste acuity thresholds significantly higher in the patients with cystic fibrosis. The impairment in taste acuity contrasts with an earlier report on taste in patients with this disease. Hair zinc levels declined as forced vital capacity of the lungs decreased as a consequence of the pulmonary disease. From the evidence presented in this investigation and in previously reported studies, zinc metabolism appears to be altered in cystic fibrosis; it is likely that impaired zinc nutriture occurs more commonly in patients afflicted with cystic fibrosis than in the population at-large.

KEY WORDS: Cystic fibrosis, Zinc, Taste acuity, Growth retardation, Trace minerals, Hair analysis.

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[1] Mention of a trademark or proprietary product does not constitute a guarantee or warranty of the product by the United States Department of Agriculture, and does not imply its approval to the exclusion of other products that may be suitable.

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INTRODUCTION

Cystic fibrosis is associated with growth retardation, delayed sexual maturation, and short stature (1). The nutritional deficiency of zinc has been assoicated with a syndrome of dwarfism and hypogonadism among rural populations of children in the Middle East (2,3) and with such clinical entitities as sickle cell disease (4) and Crohn's disease (5,6) which are also associated with retardation of growth and development in some affected children. Severe zinc depletion was found in a patient with cystic fibrosis and renal disease reported by Dodge and Yassa (7). Evidence for zinc deficiency among a population of patients with cystic fibrosis was found by Halsted and Smith (8) but not by Palin and associates (9). Interestingly, decreased plasma zinc concentration in the report by Halsted and Smith (8) was only significant in patients with "moderate to severe growth retardation" but not in patients of normal stature and growth.

Hypogeusia or impaired taste acuity has been suggested to be a pathophysiological consequence of zinc deficiency (10,11). Zinc supplementation has resulted in improved taste acuity in several studies (11-15). Taste acuity has also been investigated in patients with cystic fibrosis. Earliest publications reported *increased* taste acuity in patients with cystic fibrosis (16), but subsequent studies have reported normal or subnormal taste thresholds (9,17-20). The explicit relationship between zinc nutriture and taste acuity in cystic fibrosis has only once been investigated (9). We report here our observations on the zinc nutriture of 19 juvenile patients with cystic fibrosis with special attention to growth attainment and taste acuity.

PATIENTS

Nineteen patients, ranging in age from 6 to 17 years, were selected from among registrants at the Cystic Fibrosis Clinic of the Wyler Children's Hospital, University of Chicago Hospitals and Clinics, Chicago, Illinois. Cystic fibrosis had been diagnosed in all patients on the basis of abnormal electrolyte concentrations in sweat and a typical clinical evolution. Patients were studied during routine clinic visits. The biochemical indices of nutriture, exclusive of zinc, in these subjects is the substance of a companion report (21) and the features of vitamin A transport in these patients has been reported elsewhere as well (22).

All patients had some degree of chronic pulmonary disease but were free of clinically apparent acute infections on the day of study. None had a history of any neurological disorder that could have accounted for cranial nerve abnormalities. All but two patients were receiving replacement therapy with pancreatic enzymes to compensate for pancreatic insufficiency. We obtained informed consent from the patients and their parents after explaining the nature, purpose and risks of the study in full. Forty adolescent controls from a private day-school were studied after prior written consent had been obtained from the students' parents.

METHODS

Post-prandial blood samples were drawn between 10 a.m. and noon from

all subjects. Samples were drawn into plastic syringes, placed in plastic, trace metal-free containers containing zinc-free oxalate anticoagulant, and centrifuged promptly. Hemolyzed samples were not used for zinc analysis. Zinc was measured by flame atomic absorption spectrophotometry after the method of Sinha and Gabrieli (23). Hair was taken from the occipital scalp with stainless steel scissors. The proximal 2-3 cm were analyzed after being cut into pieces less than 1 mm in length and washed with acetone, ether, and detergent after the method of Klevay (24). Samples of 15-20 mg were then wet-ashed with nitric and sulfuric acids. The digestate was diluted to 5 ml, and zinc was measured via flame atomic absorption spectrophotometry with 5 volume percent H_2SO_4 matrix for both samples and calibration standards. Digestates of the two brands of pancreatic enzymes (see below) were also analyzed by atomic absorption spectrophotometry to determine their zinc content.

Taste acuity was assessed by the modification of the three-drop, forced-choice dilution technique published by Hambidge et al. (11). In this procedure, tastant solutions representing salty (sodium chloride), sweet (sucrose), bitter (urea) and sour (hydrochloric acid) taste qualities were employed. The concentration matrix is illustrated in Table I. For each dilution, 3 drops were presented to alternate sides of the tongue in a changing order; two drops were distilled, deionized water, and one was the tastant solution. The subject was asked to identify which drop was different from the water; this constituted taste *detection*. The subject was also asked to identify its taste quality; this constituted taste *recognition*. From these responses, detection and recognition thresholds for the individual tastants were calculated. For the purpose of statistical manipulation and comparison, the taste threshold patterns were given a quantitative numerical score by assigning a value of *minus* one for each of the tastant dilutions which could not be correctly distinguished from water (detection score), or by assigning a *minus* one for each error in detection and each error in recognition (combined detection/recognition score).

TABLE I

Concentrations of Tastant Solutions in mmoles

NaCl	30	60	90	150	300
Sucrose	15	30	60	150	300
Urea	120	150	300	500	1000
HCl	3	6	15	30	60

Pulmonary function tests including forced vital capacity (FVC) and the first-second forced expiratory volume (FEV_1) were performed with a Pulmonar^R spirometer (Jones Medical Instrument Company, Oakbrook, Illinois).

Height-for-age percentiles and weight-for-age percentiles for each patient were calculated from the anthropometric scales of the Iowa Child Welfare Research Station and the Stuart curves of the Harvard School of Public Health.

The Student "t" test was used for statistical comparison of mean values between groups of patients or between patients and controls. Simple linear regression analysis was used for calculation of correlation coefficients in the analysis of intragroup data.

RESULTS

The values for age, sex, height-for-age, weight-for-age, pulmonary function tests, and the number of capsules of pancreatic enzymes[6] taken per day are given in Table II. Ten of 19 patients had heights at or below the 10th percentile with 3 at or below the 3rd percentile; in 13, weights were at or below the 10th percentile with 11 at or below the 3rd percentile. Thus, consistent with earlier observations (1) cystic fibrosis patients show a greater relative retardation in weight than in height.

Plasma and Hair Zinc: The mean plasma zinc concentration for the cystic fibrosis group was 71.7 ± 12 µg/dl (mean ± 1 SD) and did not differ significantly from the 78.6 ± 17.7 µg/dl of the adolescent controls. Differences in hair zinc content, however, were highly significant (Figure 1). The mean hair zinc concentration for the cystic fibrosis group was 117 ± 36 µg/g and for the control group was 162 ± 23 µg/g ($p<0.001$). In addition, 8 or 18 patients had levels of hair zinc which were below the entire concentration range of the control group.

TABLE II

SOME CLINICAL CHARACTERISTICS OF THE CYSTIC FIBROSIS PATIENTS STUDIED

Patients		Growth Attaintment		Pulmonary Function		Treatment
age	sex	height percentile	weight percentile	F.V.C.† % of predicted	F.E.V.1* / F.V.C.	enzyme caps per day
6y 1m	M	90th	75th	81	78	7
7y 0m	M	80th	90th	82	71	5
8y 3m	F	10th	5th	N.A.¶	N.A.	10
9y 0m	M	35th	30th	79	93	12
9y 5m	M	<3rd	<3rd	71	75	10
9y 5m	M	50th	25th	88	75	12
9y 9m	M	25th	3rd	100	55	3
11y 2m	F	10th	<3rd	92	76	10
11y 3m	F	5th	<3rd	70	66	20
11y 10m	M	15th	<3rd	48	67	26
12y 0m	M	3rd	<3rd	78	43	9
12y 0m	F	50th	<3rd	41	54	16
12y 7m	M	10th	10th	63	71	28
12y 8m	F	10th	20th	98	77	0
13y 6m	M	15th	10th	80	78	15
14y 3m	M	<3rd	<3rd	73	57	12
14y 11m	F	3rd	<3rd	61	53	3
16y 9m	F	15th	3rd	54	45	10
17y 11m	M	10th	3rd	95	88	0

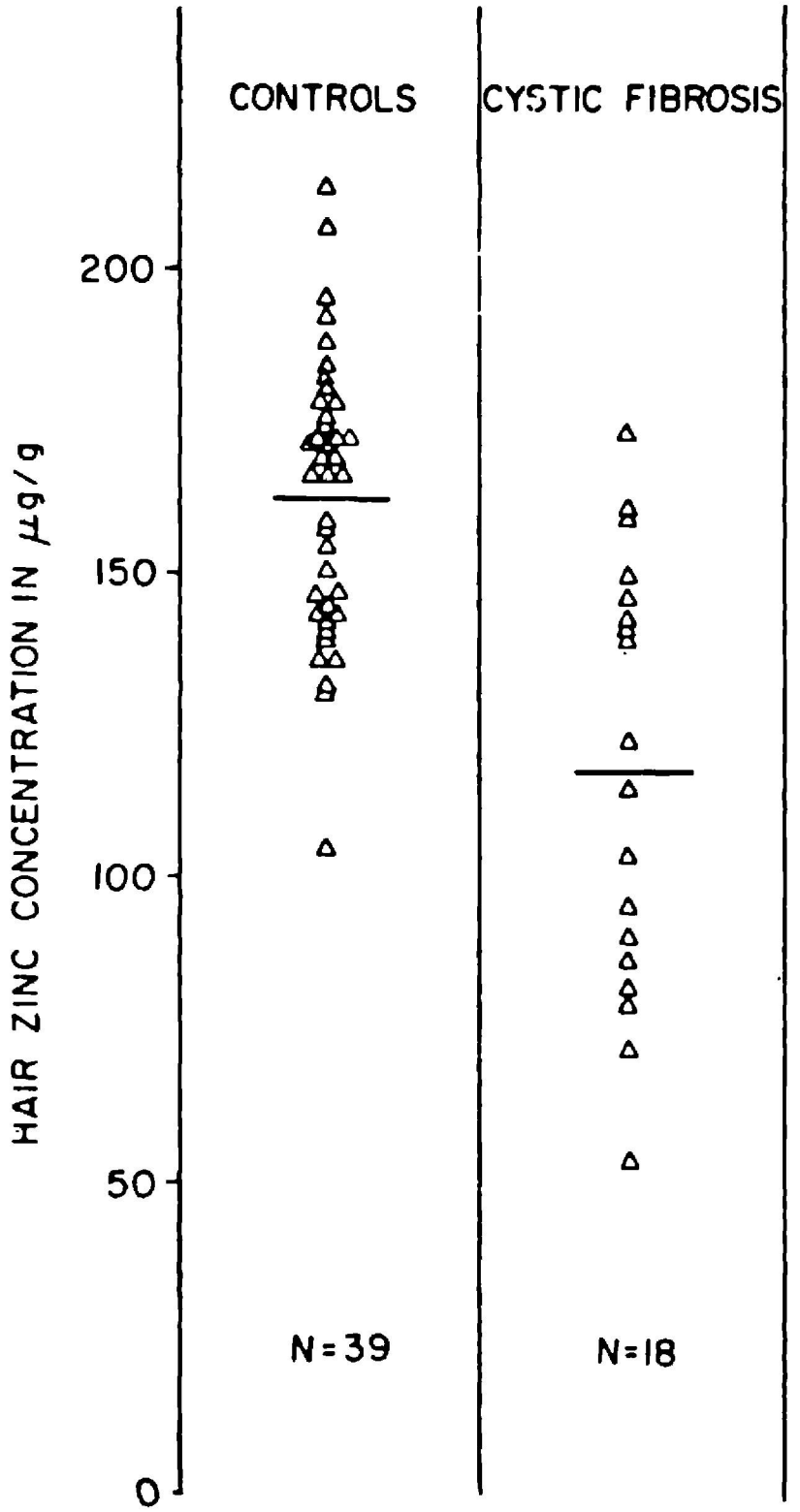
† F.V.C. = forced vital capacity

* $F.E.V._1$ = 1-second forced expiratory volume

¶ N.A. = not available

[6] Viokase® (Viobin Corporation, Monticello, Illinois), or Cotazyme® (Organon, Inc., West Orange, New Jersey).

FIG 1



Hair zinc concentrations in healthy adolescent controls and in cystic fibrosis patients.

The mean plasma and hair zinc concentrations for the cystic fibrosis group, arranged by growth percentiles, are shown in Table III. The standards to classify "moderate to severe growth retardation" used to stratify their population of patients were not reported by Halsted and Smith (8). We arbitrarily used height at or below the 10th percentile and weight at or below the 3rd percentile as our criterion for biologically significant deficits in linear and ponderal growth, respectively. As seen in Table III, none of the differences between these rather small, but evenly divided, sub-

groups was significant although there is a *suggestion* of a trend toward lower mean plasma zinc concentration in the underweight patients. Linear regression of height of weight percentiles with hair or plasma zinc concentration failed to show statistically significant correlation coefficients.

TABLE III

Mean ± One Standard Deviation of Zinc Data According to the Patients' Weight and Height Percentiles

		plasma zinc concentration (µg/dl)	hair zinc concentration (µg/g)
weight percentile	≤ 3rd	68.4 ± 11.4	122.5 ± 37.2
	≥ 3rd	77.0 ± 11.0	110.8 ± 34.7
height percentile	≤ 10th	72.4 ± 13.1	126.8 ± 30.0
	≥ 10th	72.0 ± 11.1	107.8 ± 39.8

Taste Acuity: Using numerical scoring, we found that taste acuity thresholds were significantly lower for controls than for patients (Figure 2). The mean taste detection score was 1.7 ± 1.3 for patients and 0.8 ± 1.0 for the controls ($p<0.02$); the combined taste detection and recognition scores were 5.4 ± 2.8 and 2.9 ± 2.4 for the patients and controls, respectively ($p<0.001$). The majority of the errors among the patients were with the sour and bitter tastants. Only 2 of 18 patients tested failed to detect the lowest concentration of NaCl and only 5 of 18 failed to detect the lowest concentration of sucrose.

Clinical Correlates: To determine whether or not any significant correlation between zinc status and clinical impairment attributable to the underlying cystic fibrosis could be discerned, linear regression of hair zinc, plasma zinc and taste score with height, weight, pancreatic enzyme capsule requirement, FEV_1, FVC and the FEV_1/FVC ratio were performed. The only statistically significant correlation was between hair zinc and FVC, the index of restrictive pulmonary disease ($r = 0.534$; $p<0.05$).

Zinc Content of Pancreatic Enzyme Preparations: The zinc concentration in Viokase^R capsules was 145 ± 2 µg/g (mean ± SD: N = 3) giving each capsule a zinc content of 51 µg. The zinc concentration in Cotazyme^R capsules was 112 ± 1 µg/g (N = 4) giving each capsule a zinc content of 55 µg. The greatest consumption of pancreatic enzymes was 28 Viokase^R capsules per day. This would have contributed 1.4 mg of zinc in addition to the dietary intake. This is equivalent to one-seventh to one-eleventh of the child or adolescent daily allowance for this nutrient.

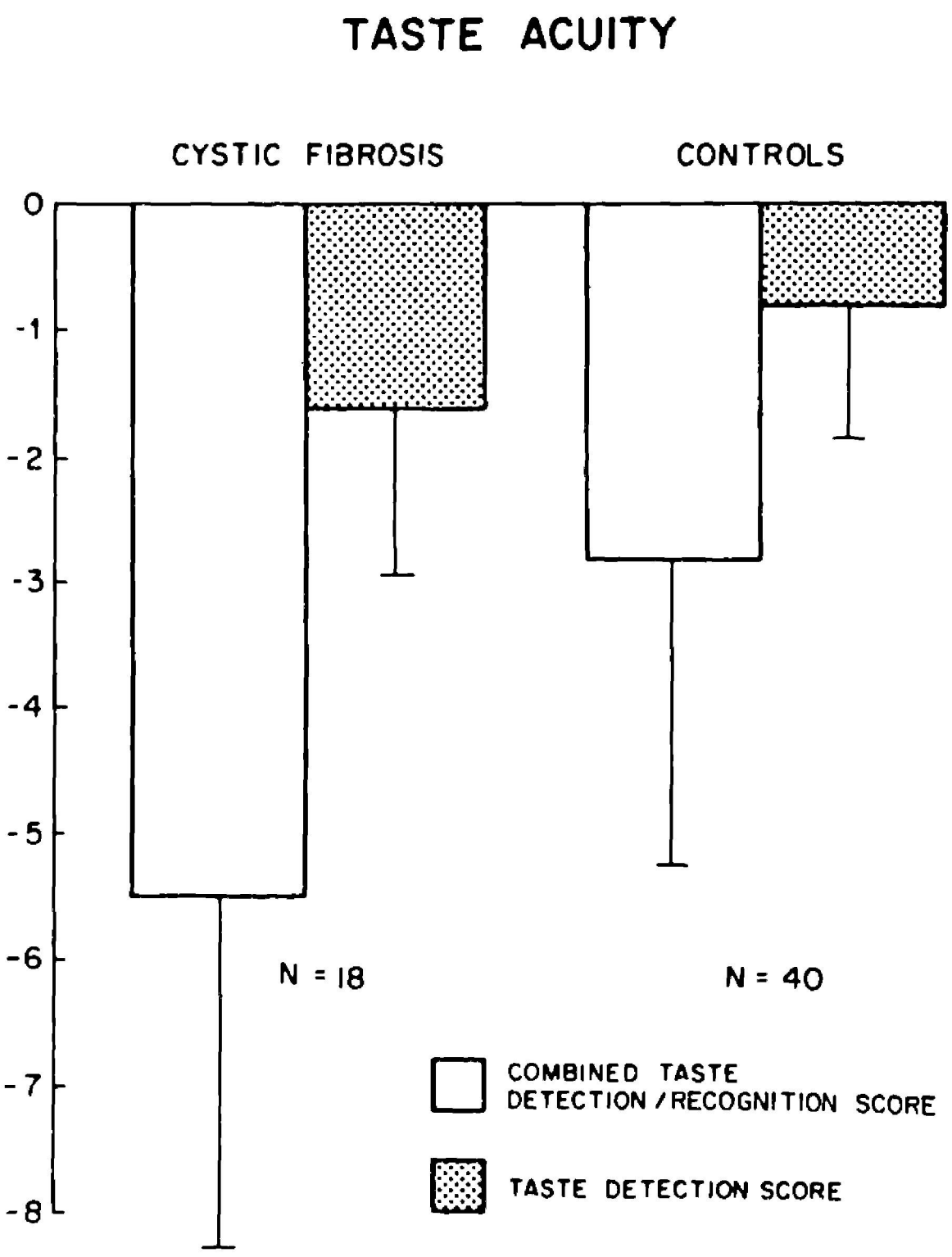


FIG 2

Combined taste detection and taste recognition scores and simple taste detection scores for cystic fibrosis patients and healthy adolescent controls. Mean + 1 SD is represented.

DISCUSSION

Our findings add to the converging evidence that zinc metabolism is disordered in cystic fibrosis (8,9,22,25-27). A problem in assigning a precise description to zinc status in this disease is the lack of reliable assessment tools for defining zinc nutriture. In the past, plasma and serum,

erythrocytes, hair, sweat, saliva, skin, and urine have been used for static tissue or body-fluid determinations of zinc concentration; no one of these indices can be considered unequivocal in reflecting total-body zinc status (28). We included two determinations plasma zinc and hair zinc concentration, in our nutritional evaluation of our patients and controls. Physiological disorders in human zinc depletion include depressed activity of zinc metalloenzymes, impaired wound healing, decreased immune responsiveness, nightblindness, and hypogeusia (28). From these, we chose taste acuity as a potential *functional* index of zinc nutriture.

As in the report by Palin et al. (9), we found no significant difference between the plasma zinc concentration of patients and controls. However, in contrast to the findings of Palin et al. (9) who also found no differential in taste acuity or hair zinc, we found a significantly lower taste acuity score in our patient group, and 10 of 18 patients had hair zinc concentration below the normal range. Palin et al, (9) went on to supplement their patients with 50 mg of zinc sulfate or a zinc-free placebo for 8 weeks. No influence on growth or in clinical indices of zinc nutriture was detected. This latter finding is not unexpected in the absence of strong indications that zinc deficiency was initially present among their clinic population. Our data provide evidence that in *some* juvenile outpatients with cystic fibrosis, zinc nutriture is indeed impaired.

Halsted and Smith (8) found diminished levels of plasma zinc in growth-retarded cystic fibrosis patients. Palin et al. (9) analyzed their plasma zinc data by stature and failed to find an association. We have also been unable to confirm any significant reduction in plasma zinc among growth-retarded patients although a *trend* toward lower zinc concentration with more weight deficit was suggested. It is curious that Halsted and Smith (8) reported that the same group of growth-retarded patients with reduced plasma zinc levels also had more severe pulmonary disease. In bacterial and other infections, leukocytic endogenous mediators (LEM), derived from stimulated neutrophils and macrophages, promote a rapid redistribution of zinc from the circulation into the liver (29,30); we have shown that LEM activity is partially responsible for the lowered zinc concentration in the plasma of hospitalized patients with inflammatory bowel disease (31). The differences observed by Halsted and Smith (8) in plasma zinc concentration between normal stature and growth-retarded patients might have been caused by active or smoldering lower respiratory infections in the latter group. None of our patients was clinically infected at the time of study. Thus, the data available can neither support nor disprove the hypothesis that zinc deficiency is a major cause of the growth retardation observed in cystic fibrosis. The present findings suggest that zinc deficiency is one of several possible contributing factors that might act individually or in concert with other nutritional and non-nutritional factors to retard linear growth or weight gain in this disease.

The significant correlation between restrictive lung disease and low hair zinc might reflect the resultant tissue depletion from previous recurrent episodes of pulmonary infection. Thus, as pulmonary disease advances zinc nutriture may become progressively impaired. It is of note that a significant correlation between FVC and *increasing* copper concentration was found in these patients (21). We found no clinical correlations with the pancreatic enzyme requirement, and we confirm the observation by Palin et al. (9) of an insignificant contribution to total dietary intake of zinc from the zinc content of pancreatic extract capsules.

The effect of cystic fibrosis, *per se*, on taste acutiy is unresolved. Conflicting observations have been reported in patients with this disease. Henkin and Powell (16) studied all of the four basic qualities of taste - salt, sweet, bitter, and sour - in cystic fibrosis patients and age-matched controls; using a variant of the forced-choice dilution technique in which volumes of tastant solutions were sipped and tasted, they found *hyper*geusia

or markedly reduced taste threshold (increased acuity). Concentrations as low as 10^{-5} M were used. Hertz et al. (19) employing identical procedures to those of Henkin and Powell (16) were unable to confirm the observation of hyperquesia; the sensitivity of children with cystic fibrosis fell within the normal range. This was also the general experience of others (9,17,18, 20). In our design, we used a three-*drop* test,and did not present concentrations of NaCl below 3 X 10^{-2} M. Thus our methods are not strictly comparable to those applied by Henkin and Powell (16) and Hertz et al. (19). Moreover, the majority of decreased taste detection and taste recognition among our patients was experienced with the bitter (urea) and sour (HCl) tastant solutions, reflected in the significant reduction in the *composite* scores for this group. Hertz et al. (19) have noted that the higher basal concentrations of sodium in the saliva of patiens with cystic fibrosis might perturb taste perception, and suggest that as a caveat in taste evaluation in this disease. Furthermore, vitamin A deficiency is known to affect taste acuity. The fact that 8 of our patients had plasma vitamin A concentrations below 30 µg/dl (21,22) might have independently influenced taste acuity. Palin et al. (9) found no improvement in taste acuity with zinc supplementation of their patients, but none exhibited initial hypogeusia. A deeper insight into the relative zinc-dependence of the reduced taste acuity of our patients might have been achieved through zinc supplementation of our population. This was, unfortunately, beyond the scope of our experimental design.

The pathogenesis of impaired zinc metabolism and zinc deficiency in patients with cystic fibrosis is unknown and remains a matter for speculation. Based on specific clinical features of cystic fibrosis, however, we can postulate several mechanisms that might contribute to derangement of zinc metabolism. The first is the possibility of excessive urinary zinc loss from recurrent pulmonary infection in addition to its redistribution under the influence of LEM discussed above. Secondly, infection places additional stress on anabolic recovery processes and might increase the dietary requirement for zinc. Thirdly, a low-molecular-weight zinc-binding factor (ZBF) that facilitates zinc absorption has been indentified in pancreatic juice of experimental animals (32). Although most of our patients were taking pancreatic extracts to correct the pancreatic exocrine deficiency, the adequacy of ZBF in these preparations or in endogenous secretions is unknown. Lack of ZBF may be responsible for the observed malabsorption of zinc in cystic fibrosis (25).

CONCLUSION

To present study failed to confirm two findings previously reported for cystic fibrosis: 1) we failed to observe a depression in plasma zinc in growth-retarded patients; and 2) we did not encounter decreased taste thresholds. However, hair zinc and taste acuity data do suggest an incidence of zinc deficiency among individual patients in a population of juvenile cystic fibrosis attending a specialized outpatient clinic. Although zinc supplementation of cystic fibrosis patients has been reported previously (9), there was insufficient indication of *pre-existing* zinc deficiency in that population to raised expectation about dramatic effects. In the context of the present findings, the therapeutic implications of zinc administration to *zinc-deficient* patients with cystic fibrosis remain to be explored.

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